



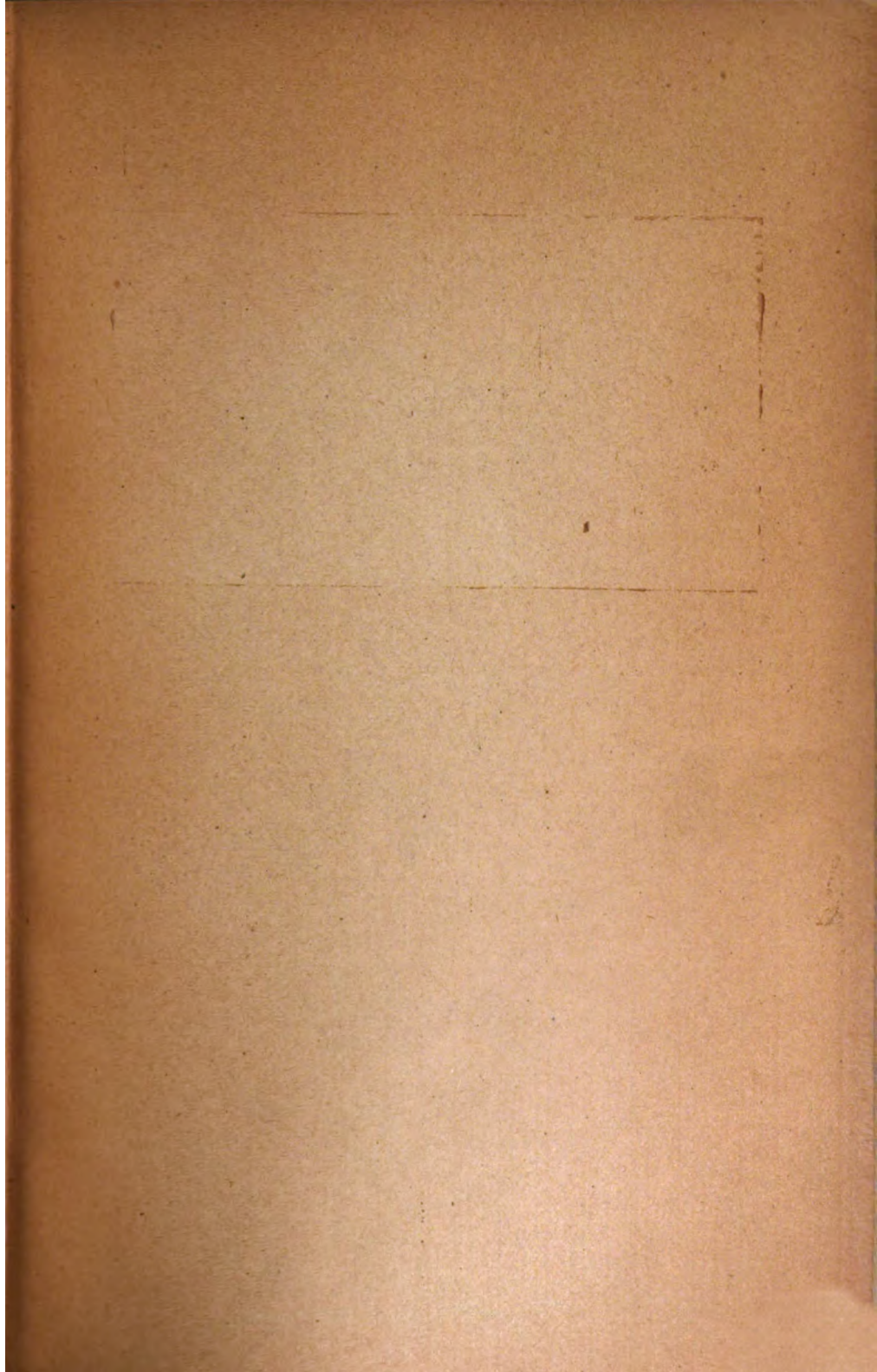
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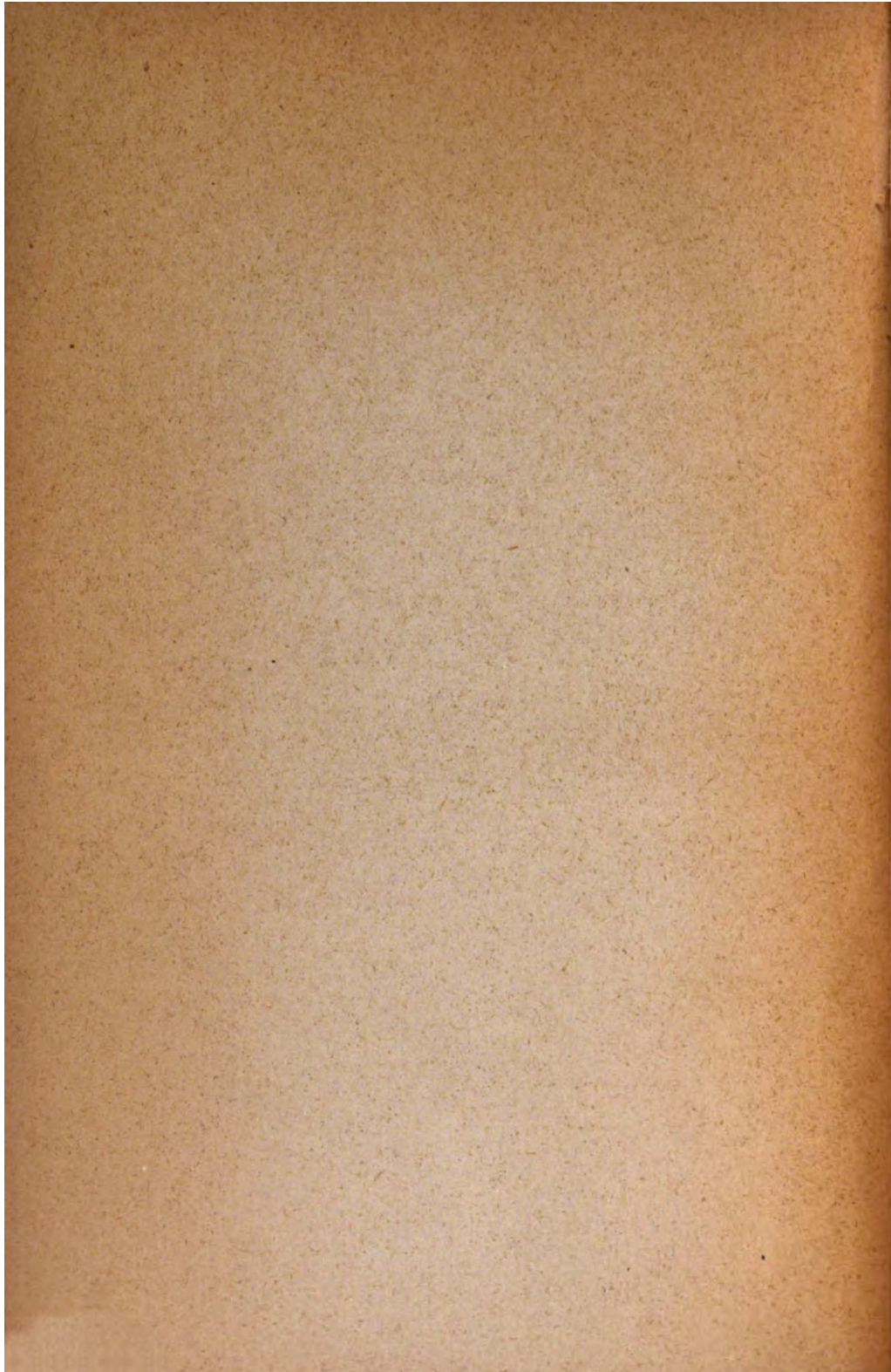
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THE THYMUS GLAND AND THE STATUS LYMPHATICUS.

By

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INTRODUCTION.

"So soon as men get to discern the importance of a thing they do infallibly set about arranging it, facilitating it, forwarding it, and rest not till in some approximate degree they have accomplished that."

In these words, taken from Thomas Carlyle's lecture on "The Hero as a Man of Letters," Mr. Bellamy Gardner opened a recent discussion of the subject of Lymphatism at the section of Anæsthetics of the Royal Society of Medicine (i.) at which a plea was raised for the appointment of a committee to consider the whole subject. That such a consideration by a responsible body is necessary at the present time, few will deny.

The thymus gland, so called from its fancied resemblance to a thyme leaf, has for many years excited interest and investigation, and for nearly a century the literature has been filled with discussion as to the significance of its enlargement. It is but very rarely absent at birth in man, except in some acephalic monsters. Von Bischoff (ii.) and Clark (iii.) report instances of such absence. Normally, the growth of the gland continues absolutely and relatively to the body weight, up to the age of two years. The rate of growth then

diminishes, and before puberty degeneration commences. This decline in growth has been said to coincide exactly with the diminution of the number of lymphocytes in the blood, and to be an index of steady diminution in functional activity of adenoid tissue generally. Complete disappearance is uncommon, traces of lymphoid tissue and a few Hassal's corpuscles being usually found in the fatty and connective tissue in the superior mediastinum.

The above is the view which has been held until recently, but lately, Bovaird and Nicoll (iv.) from a large body of evidence state that the accepted doctrine of the progressive growth up to the second year, and the subsequent atrophy, must be abandoned.

The gland occasionally persists throughout life, and in particular is associated with exophthalmic goitre, myasthenia gravis and epilepsy. An interesting case of persistent aberrant thymus is reported by Sharp (v.) in which a woman, aged 24, came for a tumour in her neck, the size of a small orange, which had first attracted attention when she was 11 years of age. There is evidence that early atrophy is found in marasmic conditions, and in any chronic wasting disease (vi.).

The thymus persists throughout life in the frog, and is found abnormally large in some anencephalic monsters.

DEVELOPMENT.

The thymus arises from the third branchial cleft, represented in the adult by the space in front of and on each side of the epiglottis.

It originates, like the thyroid, from hypoblast, and grows as a diverticulum from the foregut. These hypoblastic cells form Hassal's corpuscles. The lymphoid tissue by which they are invaded and ultimately surrounded is mesoblastic.

The gland is remarkable in appearing under three different forms (vii.):—

Primary—Composed of glandular epithelial cells.

Secondary—Composed of lymphadenoid tissue.

Thirdly—Composed of fat.

In higher animals, at birth, the only remains of the primary state are Hassal's corpuscles.

The lymphadenoid tissue commences to develop and remove the primary cells about the fourth month, and reaches its fullest development at birth.

ANATOMY.

The gland consists of two symmetrical lobes, enclosed in a firm capsule. Normally, the main mass of the gland lies on the great vessels just above the heart, and extends upwards slightly above the manubrium sterni, to within 3 or 4 c.m. of the thyroid. Below it covers the pericardium to a greater or lesser extent. When large it entirely covers the heart, and may reach the diaphragm. Laterally it reaches the roots of the lungs.

Accessory thymus glands are sometimes found. This is of importance in relation to the experimental removal of the gland. Remarkable variation is found in the weight of the gland. In nearly 500 glands of consecutive dead children, tabulated by Bovaird and Nicoll (iv.), the extremes were 0.7 grm., at three months old, and 33 grms. at fourteen months. They found that 6 grms. represented the average weight at autopsy. Such wide fluctuations are not seen in any other organ in the body, and are said by Friedleben (viii.) to be accounted for by the state of the nutrition of the body.

Most authors agree that at birth the gland measures about 5 by $3\frac{1}{2}$ by $1\frac{1}{2}$ c.m.

Dudgeon (ix.) in his monograph, "A Contribution to the Study of the Thymus Gland," records the examination of the thymus in 111 cases. In 95 of these the gland weighed less than 7 grms., or about a quarter of an ounce. In the remaining 16 cases, which died suddenly, the average weight of the gland was 25 grms.

The weight at birth is variously given. According to Morris it is 15 grms., while Quain and Testut give 5 grms. According to Friedleben a weight of over 10 grms. is pathological; of

25 cases of all sorts under $2\frac{1}{2}$ years reported by Thursfield (x.) the weight in the majority was 6 or 7 grms., while in only two cases was it 9 grms.

In Dudgeon's opinion the average weight of the gland from birth up to two years is, roughly, 7—10 grms., and he thinks that all cases in which the thymus retains its infantile size beyond the normal period of retrogression must be regarded as instances of relative hyperplasia or hypertrophy.

FUNCTION.

In spite of many experiments, little is known of the function of this organ. Kollicker (xi.) first showed that it took part in the formation of leucocytes, and Beard (xii.), working on the skate, has demonstrated the origin, from the thymus epithelium, of the first leucocytes.

For a relatively long period of development the blood contains nucleated red cells and no leucocytes. The thymus has not yet been shown to possess any properties peculiar to itself. It appears to have the function of a lymph gland; for in the embryo, which possesses no lymph glands, it is functionally active, and in reptiles and amphibia, which also possess no lymph glands, it is a permanently functioning organ. Indeed, according to Abelous and Billard (xiii.) extirpation in the frog is fatal.

As from any other widely cellular organ, a tissue-fibrinogen can be extracted from the thymus, which causes intravascular clotting, when injected intravenously. The conclusions arrived at by Svehla (xiv.), who worked on dogs with thymic extract, are as follows:—

(a) That the blood-pressure falls from paralysis of the vaso-constrictors.

(b) That the pulse rate increases, due to a direct influence on the heart.

(c) That after large doses excitement occurs followed by dyspnoea and collapse, which ends in death.

The possibility is thus established that some of the cases of so-called thymic asthma in children may be due to excess of thymic secretion in the blood.

It is stated by Mendel (xv.) that the thymus is intimately connected with the proper development and growth of bone, and that the symptoms of rickets are due, in fact, to disturbance of the gland's function. He thinks that enlargement of the spleen in rickets may be regarded as vicarious hypertrophy. For the reason above he treats rickets with thymus gland.

RELATIONSHIP OF THYMUS TO SEXUAL ORGANS.

Henderson (xvi.) states that castration causes a persistent growth or a retarded atrophy of the thymus in cattle, rabbits and guinea-pigs: so that ox-thymus is much larger than bull-thymus of the same age.

Noel Paton (xvii.), speaking of the influence of removal of the thymus on the growth of the sexual organs, discusses a possible reciprocal action between thymus and testis, each checking the other's growth. In guinea-pigs he found that removal of the thymus seemed to be followed by a more rapid growth of the testis, and he wondered whether testicular growth could be governed by some internal secretion of the thymus.

Vincent (xviii.), on the contrary, found that removal of the thymus in the guinea-pig did not in any way affect the animal

HISTORICAL.

The term *status lymphaticus* owes its origin to Paltauf (xix.), who in 1889 demonstrated the condition as a pathological entity. As early as 1614, Plater (xx.) called attention to the connection between enlargement of the thymus and sudden death, and about 1830, due largely to the teaching of Kopp (xxi.), the theory of the etiological relationship of thymic hypertrophy and laryngospasm, gained widespread credence. When death occurred from syncope, associated with an enlarged thymus, it was said to be "*Thymus Tod.*"

Friedleben's (viii.) investigations in 1858 overthrew these earlier views, and in 1884, Somma showed the first case of death proved to be due to pressure by the gland. In 1888, Grawitz (xxii.) directed renewed attention to the possibility of compression, and detailed two cases. Many followed, until in 1889 Palttauf (xix.) advanced his theory of a lymphatic condition under the name "status lymphaticus," and denied the mechanical theory. Of rational explanations, that of pressure of the enlarged thymus was the theme of much controversy, being ardently supported by Recklinghausen (xxiii.), Grawitz (xxii.), and others. The theory was plausible and fortified by indisputable records in which pressure was evident. Friedleben emphatically denied this, and he was supported by Scheele's report which stated that the trachea remained uncompresssed by a weight of 50 grms.

CONSIDERATION OF THE SEPARATE FEATURES OF STATUS LYMPHATICUS.

For many years, and from cases of a variety of abnormal conditions, observers have accumulated evidence upon which is based the present knowledge of status lymphaticus. The wide scope of these observations affords strong evidence that this condition represents an important fact in pathology. The anatomical features which are believed to characterise the subjects of status lymphaticus include hypoplasia of the heart and aorta with partial or general hyperplasia of the lymphatic organs, the spleen, thymus, lymphatic glands and the red marrow. There is also, very commonly, evidence of rickets. Enlargement of the thyroid appears so frequently in the reports of recent cases that it has been thought by some to have a direct bearing upon the conditions under discussion.

It has long been apparent that a systemic weakness is inherent in patients suffering from such various complaints as chlorosis, leukæmia, hæmophilia, thyroid enlargement, with or without Graves' disease, thymus enlargement, rickets, or chloroform narcosis, and this weakness renders the subject liable

to sudden heart failure, in the presence of apparently inadequate exciting causes.

Hypoplasia of the Heart and Aorta.—This was one of the earliest conditions studied, and first claimed by Virchow in 1872 to be the fundamental pathological condition in chlorosis. It was known to be frequently associated with certain other abnormalities in the blood and blood vessels. The diminished vital resistance of such subjects and their liability to secondary organic diseases were regularly noted by writers between 1860 and 1880, and special contributions, with illustrative cases, were made by various authors. More recently, Leyden and others have pointed out the frequent connection of arterial hypoplasia with cardiac disease.

Virchow's theory of the origin of chlorosis was supported and further extended to hæmophilia by the observations by Copeland (xxiv.) and Bamberger (xxv.), of the coincidence of both of these diseases of the blood with congenital narrowing of the aorta. Otto (xxvi.) and Rokitsansky (xxvii.) noted the frequency with which this anomaly was associated with hypoplasia of other tissues and organs. Recklinghausen (xxiii.) found a general infantile grade of development in a woman of 25, dying of phthisis, and showing, in addition to hypoplasia of the heart and aorta, a patent foramen ovale, a persistent thymus, lobulated kidney and infantile pelvis and sexual organs.

The diminished resistance of the subjects to infectious diseases has been observed in cholera, in pneumonia and in typhoid fever. In two cases of sudden death during convalescence from typhoid, Hiller (xxviii.) found uniform narrowing of the aorta. Such miscellaneous observations might be multiplied at length, but sufficient evidence has been reviewed to show that hypoplasia of the heart and arteries, which is a prominent anatomical feature in the status lymphaticus, is often of itself an evidence of a congenital defect in physical development, and indicates a diminished vital resistance in the organism.

The existence of this abnormality may be claimed as a probable ground for the belief that the subjects of the status lymphaticus possess inferior vital resistance.

Hyperplasia of the Lymphatic Organs.—This forms a more recent contribution to the study of diminished vital resistance, and the demonstration of its essential importance has served to correlate many facts previously known and to justify the employment of the old term, *constitutio lymphatica*, revived by Paltauf for the general condition. That some underlying constitutional defect must be assumed to exist, in order to account for the many sudden deaths usually referred to the pressure of an enlarged thymus upon the trachea, bronchi or great vessels, was the conclusion reached by Paltauf (xix.) and others from a long experience of this class of case in Vienna. Since the time of Friedleben, who in 1858 denied that a normal or hypertrophic thymus could produce fatal laryngismus, there has been constant discussion as to the manner of death in many cases of sudden death without apparent organic cause other than enlargement or persistence of the thymus, nor are opinions as yet in agreement on this subject. Many writers still claim that death in these cases is produced either by direct pressure of the enlarged thymus upon the bronchi or great vessels, or by reflex cardiac or respiratory paralysis arising from the thymus. Of such writers may be mentioned Recklinghausen (xxiii.), Nordmann (xxix.), Gluck (xxx.), Pott (xxxi.), Seydel (xxxii.), Grawitz (xxxiii.), and Benecke (xxxiv.), and their reported cases indicate that under some circumstances the pressure from an enlarged thymus may reach a dangerous degree. Only a small percentage of deaths would, however, be explained on such a basis, as the patients usually die very suddenly, and the hypertrophy of the thymus is often inconsiderable. Ewing, indeed, declares that the condition may exist without enlargement of the thymus.

The following meagre note of a case of fatal compression of blood vessels by a large thymus is found in vol. xiv. of the Transactions of the American Pediatric Society. "The infant was six months old, and during life was occasionally slightly cyanotic and had spells of rapid and laborious breathing. On two occasions it had convulsive seizures. Auscultation revealed

a loud systolic murmur at the base of the heart with the valve sounds clear and distinct. The murmur was not transmitted in any direction. The infant died suddenly, and the autopsy showed, as was expected, a large thymus gland measuring two inches in length and one inch across. The lower pole of the gland compressed the large vessels in such a way as to cut off the circulation."

The observations of Paltauf convinced him that many of these fatalities, especially in infants, must be referred to a capillary bronchitis, of which the post-mortem evidences are often very meagre, and the observations of Hoffmann and Kolisko (xxxv.) have led them to believe that all the others are referable to a peculiar constitutional defect, of which an expression is to be found in general hyperplasia of the lymphatic structures. In the experience of these observers, the enlargement of the thymus in these cases is only one feature of a general lymphatic hyperplasia, involving also the spleen, the tonsillar ring, the thoracic and abdominal lymph glands and sometimes the bone marrow; moreover, an examination of the cases of "Thymus Tod," reported by earlier writers, even those of Friedleben, discloses the fact that in the majority of cases it was noticed that the tonsils, spleen and lymph glands were more or less hypertrophic, although no particular significance was attached to this fact at the time.

The same observers noted a similar condition of general hyperplasia of the lymphatic structure of the body in a series of sudden deaths under chloroform narcosis, and the study of these cases, which have recently been collected by Kundrat (xxxvi.), together with reports of similar cases from other sources, renders it possible to give a somewhat detailed description of the pathological changes in the enlarged organs and of the other characteristics found at autopsy in these cases.

Pathological Changes in the Lymphatic Structures.—The thymus frequently measures from 6 to 10 centimetres in length, reaching at times from the isthmus of the thyroid to the heart's apex. Its consistence may be increased, or it may exude

on section a milky white fluid ; it has been found adherent to the pericardium, and often encircles the great vessels more or less completely. The amount of blood in the organ is often found increased, and its surface, on section, may present the petechiæ characteristic of death from asphyxia. The histology of the enlarged gland indicates usually a simple hyperplasia of the lymphoid cells, enlarging and multiplying the follicles, sometimes causing a deposit of small nodules of lymphoid cells in the centres of the lobules, in the trabeculæ, or even in the outlying adipose tissue.

The enlargement of the spleen is of moderate degree, and is referable to a simple hyperplasia of the lymphoid elements with hyperæmia. The enlarged Malpighian bodies, being usually devoid of blood and light coloured, are prominently marked off from the hyperæmic pulp, giving an appearance not unlike that of miliary tubercles. In some cases the lymphoid cells are so much increased as to infiltrate the splenic pulp, and the microscopical outlines of the follicles are then indistinct. The pulp cells may contain an increased deposit of blood pigment.

In addition to the pharyngeal, thoracic and abdominal lymph glands, the faucial and lingual tonsils are nearly always enlarged. From the latter the infiltration may involve the epiglottis and sinus pyriformis. The cervical, mediastinal and axillary glands may be moderately enlarged. Biechele (xxxvii.) has shown in illustrations how marked may be the elevation of Peyer's patches and the distinct aggregations in the ileo-cæcal region.

Relation to Pseudo-Leukæmia.—Such a general hyperplasia of the lymphatic structures of the body at once suggests a possible connection either with leukæmia or pseudo-leukæmia. The destruction of red blood cells, characteristic of these diseases, has been approached in cases of the lymphatic constitution, as indicated by a deposit of blood pigment in the spleen and lymph glands. Lymphocytosis has also been pointed out by several observers. But these many isolated points of resemblance con-

stitute no distinct indication that the status lymphaticus has any immediate connection with leukæmia.

In the majority of cases of status lymphaticus the enlargement of the lymph glands does not pass beyond the limit of what may be called a physiological hypertrophy, and bears little resemblance to a tumour formation. The spleen is rarely much enlarged, the presence of considerable pigment in the spleen pulp is too ordinarily seen to be interpreted positively as the result of an excessive blood destruction, such as characterises the severe anæmias; yet it must be admitted that the very considerable degree of pigment deposit reached in some cases indicates that the blood has suffered severely. These children are, however, not generally anæmic, and even those in the worst state of health do not resemble cases of leukæmia or chlorosis.

ASSOCIATION OF STATUS LYMPHATICUS WITH AN ENLARGED THYROID.

In 9 of the 17 cases collected by Kundrat (xxxvi.), and in 3 of 7 referred to by Paltauf (xix.), and in one of Ewing's (xxxviii.) two cases, the thyroid was found enlarged. Of the significance of this it is rather difficult to judge, but there is abundant evidence to show that some sympathetic relationship exists between thymus and thyroid. Beclard (xxxix.) found an enlargement of the thyroid after extirpation of the thymus, and *vice versa*, in animals capable of surviving the loss of these organs. Enlargement of the thymus has been found in Graves' disease and hypertrophy of lymphatic glands, tonsils and intestinal follicles, has been noticed in the same disease by White (xl.) and Gowers (xli.). Hale White (xlii.) has reported two cases of sudden death in Graves' disease, associated with large thymus glands, in which autopsy showed no reasonable cause of death.

The liability to sudden cardiac paralysis, which is often the prominent feature in the death of subjects of status lymphaticus, finds at least partial counterpart in the persistent tachycardia

of Graves' disease. Blake (xliii.), dealing with the surgical aspect of status lymphaticus, states, "It is impossible to say how often status lymphaticus co-exists with exophthalmic goitre, yet probably in many cases in which an hypertrophied thymus has been alone mentioned, lymphatic hyperplasia has been overlooked, and it may not be too much to say that status lymphaticus probably accounts for more sudden operative deaths in Graves' disease than is credited."

In Wynn's (xliv.) fatal cases of status lymphaticus, the thyroid showed profound changes, resembling those found in exophthalmic goitre.

Kecher has pointed out that there is constant swelling of lymphatic glands in the neighbourhood of the thyroid, and argues that the thyroid secretion is therefore competent to produce changes in lymphoid tissue. The thyroid secretion exerts a depressant action on the blood pressure, and changes in the thyroid, in status lymphaticus, may be an explanation of the tendency of the cases to sudden death. The question arises whether the changes in the thyroid are primary and the lymphoid hyperplasia secondary, or whether each results from some unknown cause. If the former is true, possibly improper feeding in infants may be the cause. Chalmers Watson has shown that the thyroid is very sensitive to alteration in diet. Many cases of status lymphaticus are associated with rickets, and there are other signs that improper feeding may be at least one cause of this dangerous condition.

Before leaving the subject, the following remarkable case which occurred in the practice of Mr. Carter Braine may be quoted. A young woman, aged 24, was being operated upon for removal of an abdominal tumour. Ethyl chloride was administered, followed by ether. Soon after the commencement of the operation the pulse became weak and the respiration shallow. The latter shortly stopped altogether. There had been no cyanosis nor stertor. The pupils were widely dilated, and there was no corneal reflex. Artificial respiration was persevered with although everyone present considered the

patient dead. During this procedure it was noticed that the thyroid gland became swollen, the lateral lobes with the isthmus being clearly seen. It is certain that this was not present during the induction of anæsthesia, nor for some time after artificial respiration had been started. The head was now flexed upon the sternum to relieve any pressure upon the thyroid by relaxing the sterno-mastoids, and artificial respiration continued in this position. In a few minutes the pupils contracted down, a thready pulse returned, and natural respirations were re-established. The operation was now completed. The thyroid swelling soon disappeared, and when the patient was put back to bed her colour and pulse were good, and no trace of the thyroid could be discovered, the tracheal rings being easily felt. There was no prominence of the eyes, nor was any tachycardia present afterwards.

Mr. Carter Braine, whose case is reported in full in the Proceedings of the Royal Society of Medicine for March, 1910, thinks that it shows conclusively that the thyroid, under certain conditions, may become so engorged as to interfere with respiration, and that in status lymphaticus under similar conditions, the thymus gland may also become engorged, giving rise to reflex cardiac inhibition or respiratory failure.

THE RELATIONSHIP BETWEEN STATUS LYMPHATICUS AND MYASTHENIA GRAVIS.

In the accounts of sudden death in association with myasthenia gravis, there is no difficulty in recognizing a strong resemblance to many recorded cases of fatal lymphatism. Dr. Farquhar Buzzard has recently summed up the points at which the two diseases seem to touch. The first point is the mode of death, and in the suddenness of this event, which is but one of the many ways in which cases of myasthenia may terminate, the two diseases resemble one another.

In referring to the second point, Dr. Buzzard speaks as follows:—"During the last ten years it has been shown that myasthenic symptoms are constantly associated with certain

morbid changes, chiefly in tissues outside the brain, spinal cord and peripheral nerves. These may be briefly summarised in the following way. In the first place, scattered throughout many of the tissues and organs of the body, and especially in the muscles, are to be found small clumps of lymphoid cells which I have termed 'lymphorrhages,' and which have the appearance of having escaped from the lymphatic circulation.

"In the second place, a careful examination of the skeletal muscles reveals a varying number of fibres undergoing degeneration. This degeneration may be slight, amounting only to slight hyaline or granular change, or may be more marked, resembling the atrophy of the early myopathies. In the third place, there is present, in probably over 50 per cent. of cases, a thymus gland developed out of all proportion to the age of the patient."

Dr. Buzzard mentions a striking exception to his own experience, and that of other observers, of finding but scanty evidence of general lymphatic hyperplasia in cases of myasthenia gravis. The case, recorded by Hödlmoser, was that of a girl with typical myasthenic symptoms, who died from respiratory trouble, and who was found post-mortem to present the features of status lymphaticus—a large thymus, prominent follicles at the base of the tongue, and hyperplasia of the lymphatic tissues of the intestines.

HYPOTHESES TO ACCOUNT FOR THE ASSOCIATION OF ENLARGED THYMUS WITH SUDDEN DEATH.

The clinical picture of "congenital stridor" is thus described by Hochsinger (xlv.):—Stridulous breathing during the first few weeks of life, without any great distress. It usually lasts for months, and disappears as suddenly as it came. No cyanosis and no dyspnoea in the true sense. No hoarseness and no catarrhal symptoms in the larynx. Harshness, of greatest intensity, at end of inspiration, because during inspiration the thymus descends into the thorax, and rises again with expiration. In thymus stenosis, inspiration only is interfered with,

the gland acting as a valve which is sucked in during inspiration. Inspiratory retraction above and below the sternum is invariably present, but not so severe as in the croup of capillary bronchitis. He thinks that these symptoms are caused by some catarrhal affection of the bronchi, which must be differentiated from capillary bronchitis and bronchial asthma, in which condition expiration is more involved than inspiration.

Paltauf believed that the hyperplasia caused lowering power of resistance and a liability to cardiac paralysis, the hyperplasia being the anatomical manifestation of a certain disordered constitutional state of a lymphato-chlorotic nature which so influenced the central nervous system that death might occur from very slight causes. It has been suggested that the symptoms arise from toxæmia, from excessive secretion of the thymus, and more recently Blumberg (xlvi.) has suggested that the lymphatic glands may cause this toxæmia. Even if the affection is toxic, however, it is yet a question whether the lymphatic enlargement is not due to toxins, and these may possibly be the result of absorption from the alimentary canal.

Dudley Buxton considers that there is a lessened power of resistance to poisons, whether thyroid, thymus or anæsthetic, and that death is due primarily to heart failure. He suggests that possibly the heart is unable to enlarge in status lymphaticus. The resemblance which the general symptoms present to struma has been observed, and a theory has been advanced that, whereas struma is considered to be a forerunner of tuberculosis, status lymphaticus may be a tubercular condition in a still more inactive form.

Fox (xlvii.), dealing with the subject in the *Lancet*, suggested that blood conditions would be found at the root of the condition. His experience in testing blood coagulation impressed him with the fluid character of the blood in lymphatic subjects. This fluidity disproves the idea that it is the entry into the circulation of thymus secretion which coagulates the blood.

Gallatti (xlvi.) notes a peculiarity of status lymphaticus, namely, a predisposition to œdema, and he holds that slight factors may incite this tendency into activity. This œdema is represented by the pasty skin, tendency to eczema and œdema of brain and lungs, which latter observations were made by Kundrat in a case of death under chloroform, by Paltauf, and by Langerhans in the case of his son's death. Piedcock is evidently of the same idea in thinking that death may be due to increased intracranial pressure, resulting in compression of the medulla, and it has been believed that such an increase of pressure is a factor in such neuroses as spasm of the glottis, tetany, infantile convulsions and epilepsy, and the various forms of sudden death incidental to status lymphaticus.

Wiesel (xlix.) puts forward a widely different theory, namely, that the symptoms are produced by disease of the chromaffin system of cells which are dispersed along the course of the sympathetic nerves, to which they belong embryologically, and which are found in largest numbers in the medulla of the adrenal bodies. In his observations on the thymus gland of 50 children, Fortescue-Brickdale (l.) found only three which would be regarded as cases of lymphatism, and he considered that these could be explained by the theory of toxin absorption, in that it is not more difficult to believe that a rapid enlargement of the thymus may occur, than that the spleen may undergo a similar process.

Dudgeon (vi.), summarising 16 cases of children who were found dead or who suffered sudden death, found well-marked rickets in most, with hypertrophy of the pharyngeal lymphoid tissue and a large thymus. The thyroid was enlarged in one case. In only three cases were splenic enlargement, enlarged solitary follicles and Peyer's patches, prominent features. Sub-plural and subpericardial hæmorrhages were seen several times. Thymic hæmorrhages were seen twice. In 8 cases purulent fluid expressed from the thymus was found to be sterile, and in one, an organism like the pneumococcus of Fraenkel was discovered. Large cells containing eosinophile granules were a

characteristic feature on the slide ; there was no distension of the right side of the heart, no thrombosis of vessels, and no tracheal stenosis. A certain small number of cases, however, have undoubtedly shown evidence of asphyxia. The number and wide variation of these different hypotheses serve to demonstrate, if nothing else, the want of accurate knowledge of the subject. Von Sury, of Vienna, indeed, in a recent review of over 2,000 autopsies in children up to 15 years old, failed to find a case in which death could be attributed to enlargement of the thymus (li.). It has been assumed by some that because the gland has been found enlarged after death, the fatal termination was caused by pressure. It would seem probable, however, that pressure would cause more gradual symptoms, unless a sudden swelling of the gland occurred, of which there is no proof. We have seen that the thyroid may undergo rapid enlargement (in Carter Braine's case), and consequently there is at least a probability that in some cases a similar change occurs in the thymus. Friedleben, experimenting on animals, failed to produce any great enlargement of the gland by causing congestion.

The theory of sudden vascular engorgement cannot be upheld by some, as the trachea, even in the youngest child, is in their opinion more resistant, and would groove the gland, and even if death was caused but fairly often by this means, there would be a greater number of occasions in which asphyxia occurred than clinical and bacteriological facts support. The convenient supposition that the heart's action is stopped by pressure of the thymus gland upon the vagus nerves is but rarely of use. It would be expected in such a case that the cervical veins would become engorged from such pressure, and this is not the case except in rare instances, such as that reported by Caille (lii.).

Walker (liii.) sums up against the theory of compression of the thymus on the following grounds:—That compression is found at autopsy only in the rarest cases. That asphyxia is not present in cases of deaths witnessed by competent observers.

Though Friedleben found untenable the theories of pressure on trachea or vagus, there is no doubt that compression exists in some at least of the published cases. Those reported by Lange (liv.) and Cleissen (lv.) will serve as illustrations. In the former, a well-nourished child, aged $3\frac{1}{2}$ years, suddenly died. The trachea was found contracted one inch above the bifurcation, so that the lumen, while not effaced, was like the hollow of a scabbard. The thymus weighed three quarters of an ounce. Lange claims this as the first recorded case of fatal thymic compression. In the latter case the thymus covered two-thirds of the heart, and was adherent to the pericardium. The trachea was found to be almost completely compressed.

A case was reported thirteen years ago by Rolleston (lvi.) in which pressure was exerted for a considerable time on the trachea and cervical vessels of a boy aged 6 by a persistent thymus which had undergone hyperplasia, and which weighed 11 ounces. It was thought possible that death was caused by a direct pressure upon the heart or pulmonary artery.

The late Dr. George Carpenter showed a specimen at the Royal Society of Medicine on November 26th, 1909, which he considered supported the theory of tracheal compression of the thymus. The clinical notes were as follows:—

A plump male baby of 10 months became suddenly sick early one morning, with rapid respirations. The same morning he was taken to hospital, where the temperature was 100° F., and the respirations 60. There was recession of the intercostal spaces; the voice was clear. The air entry was diminished all over. No râles were heard. The respirations became more embarrassed, and the child died in a few hours. The thymus was found to extend in a solid mass from the thyroid to behind the manubrium, when it split into two lobes, which extended as far as the second and third costal cartilages on the right and left sides respectively. The trachea was said to be much compressed from before backwards, just above the manubrium. The thyroid was enlarged and red. There was no general enlargement of the lymphatic glands or lymph follicles.

The lungs showed extravasation of blood into the alveoli, indicating death from suffocation. The specimen was shown mounted in a glass case, and although it was difficult, for some observers at least, to make out clearly the tracheal compression, the case would probably have been remembered by those present as one of tracheal compression by a thymus gland had it not been stated at a later date that a subsequent examination of the interior of the trachea had revealed a deposit of false membrane of diphtheritic origin.

It has been suggested that a sudden throwing back of the head may, by vascular congestion, so increase the degree of pressure as to induce asphyxia. Such a death would be comparable to that which may occur in a patient with goitre, who is anaesthetised. It cannot be denied that spasm of the glottis may play a part in some of the cases, just as it occasionally causes sudden death in laryngismus stridulus, though how an enlarged gland can excite such spasm is more difficult to explain.

Hochsinger (lvii.) considers congenital stridor to be almost exclusively due to tracheal compression. He thinks that the peculiar bruit, which is accentuated at the end of inspiration, associated with retraction of the thoracic walls, but without alteration of voice, can only be due to compression. It may be mentioned here that deformity of the epiglottis has been found to cause such stridor in several cases.

Warthin (lviii.) discussing the critical space, states that compression does occur, and quotes Flugge, who found in seven case of sudden death marked compression of the lower portion of the trachea. Marfan's case of œsophageal compression with dysphagia is also quoted. In order to demonstrate compression at autopsy, the neck organs should be examined before removal of the sternum, in the manner which he explains, or they should be fixed with formalin. Disturbance of the anatomical relations may account for many denials of the existence of pressure.

A view held by Dr. Leonard Williams and others is that status lymphaticus results from some want of balance between

the internal secretory glands. The normal balance is maintained by a mutual antagonism, as is illustrated by that of the ovary with the thyroid and suprarenal, and of the thyroid with the pancreas. According to this view, when the major glands remain undeveloped the minor glands do the work, and in the status lymphaticus it is the thyroid gland which is at fault. Dr. Williams points out that adenoid vegetations may be made to get smaller by the administration of thyroid extract, and suggests that this gland should always be tried internally before any operation is decided on. It has been suggested, and not unreasonably, that the presence of hyperplasia throughout the lymphatic system is associated with the production of toxins, and it seems consistent to believe that a toxæmia exists in such people which enables slight peripheral causes to produce cardiac inhibition.

Humphry (lix.) in a recent review of 5 cases of status lymphaticus, occurring in his own practice, leans to the theory of a toxæmia, and thinks that the respiratory centre is the first to be paralysed. He lays stress upon the fact that before compression of the trachea can occur, the innominate vessels must be implicated, and that this would show itself in some œdema of the arms.

It is possible that status lymphaticus weakens the resistance of the body to the remote as well as to the immediate toxic action of chloroform, and it may be that delayed chloroform poisoning has played a part in some of the reported cases, in which death has been avoided, during the actual administration of the anæsthetic. A case has recently occurred, in the writer's experience, at the East London Children's Hospital, which, except for the fact that death was delayed for some time, presented the usual features of the disease. An apparently healthy boy of $4\frac{1}{2}$ was anæsthetised with chloroform on a piece of lint, in order to have his hernia operated on. Shortly after the commencement of the anæsthetic, vomiting and defæcation occurred in spite of the usual precautions. The boy had not exhibited any fear of the anæsthetic. The operation had not been started.



The Thymus Gland and the Status Lymphaticus.

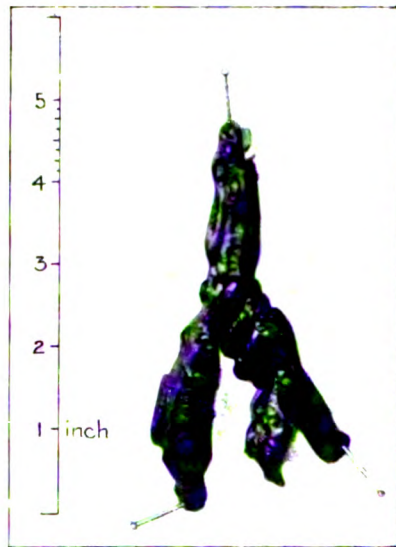


FIG I.

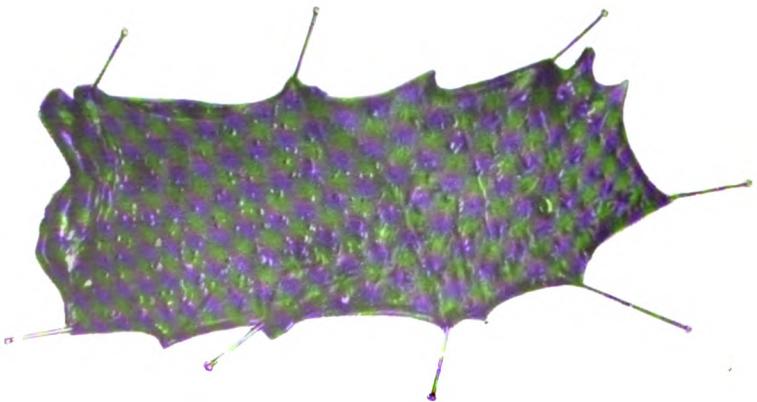


FIG II.

Cyanosis occurred and respiration ceased. Artificial respiration, with injections of ether and brandy, brought him round. Hot flannels were applied to the præcordium, causing some superficial burning of the skin. The boy was put back to bed, and rectal salines given. Consciousness was soon restored, and the boy talked to his parents and seemed fairly comfortable. He complained greatly of thirst. The pulse was not very strong, but did not cause great anxiety. The temperature the same evening was 102° F., pulse 140, respirations 82. The following day the boy was slightly sick three or four times, and during the afternoon the pulse gradually failed and death occurred. This was thirty-two hours after the anæsthetic had been given. The breath had not smelt sweet. The boy was conscious until shortly before death.

At the autopsy, which was performed by Dr. Theodore Fisher, a superficial burn was seen over the præcordium. The glands were not palpable anywhere, and the liver was not felt. The thymus was enlarged and extended over the pericardium down to the diaphragm. It weighed 12½ grms. (fig. 1). There was no evidence of tracheal compression. The trachea and bronchi were empty. The tonsils were large, but not markedly so. The lungs were normal. The aorta was small, and showed patches of atheroma below the valves as well as above them. The liver was neither large nor fatty. The spleen was not enlarged. The mesenteric glands were found to be large and discrete. The pancreas was normal. Ascarides were found in the appendix. The follicles of the duodenum and small intestine were definitely enlarged (fig. 2), and the picture of the smooth gastric mucous membrane, separated by the pylorus from the irregularly nodular internal surface of the duodenum, was very striking.

DIAGNOSIS OF STATUS LYMPHATICUS.

Of the various points brought forward by different observers towards a correct diagnosis of this condition, the more important only will be reviewed here. There would seem to be no doubt that a correct diagnosis may often be made during life, and

that the condition is not so mythical as those would have us believe who consider it an invention to cover the misdeeds of the unfortunate anaesthetist. Indeed, there are a few instances in the literature of a diagnosis of thymic enlargement having been the means of a decision against operation. It has been pointed out that too much stress must not be laid on enlargement of the thymus. In some cases of this disease the organ is not present at all, and in other cases fatty tissue replacing the thymus is mistaken for it. Dr. Spilsbury has pointed out the importance of making a thorough microscopic examination of the tissues after death. It is very difficult to say how much thymus tissue is present, and therefore records as to measurements or weight of the gland should always be placed side by side with a record of the microscopical examination. He lays stress upon the change found in the heart muscle. There is a certain degree of degeneration in all cases, and in well-marked cases a surprising degree of fatty degeneration or brown atrophy, and frequently both together.

Blumenreich (lx.) considers that dulness is an important diagnostic sign, and says that "in young children there is definite form of thymic dulness in the shape of an irregular triangle or truncated cone, whose base is the sterno-clavicular junction, and whose apex is the second rib. The sides extend but very slightly beyond the sternal margin, rather more on the left than on the right side. Dulness extending more than 1 c.m. on either side, concealing the note of pulmonary resonance between the heart valves and the normal area of thymus dulness, shows, in the absence of other causes, an enlarged thymus." Some observers consider it quite possible to percuss out the thymus by placing the body in different positions. With the body on its back very little can be percussed, but the gland may be readily mapped out over a large surface by percussing from below, with the child supported face downwards.

Hiedert (lxi.) cites the case of a child aged 15 months, suffering from croup, in whom the upper portion of the sternum was moderately projecting, and in whom the percussion note was

impaired. Tracheotomy followed the failure of intubation, and an enlarged thymus was found.

Hochsinger (lvii.) reports a series of 58 radiograms in nursing infants. In 26, hypertrophy was demonstrated, and 20 of these showed the typical picture of congenital stridor. Dilatation of the left ventricle, which usually results from narrowing of the aorta, is sometimes found. As already mentioned, hypoplasia of the heart and arteries is frequently associated with an infantile or defective development of other organs and tissues, especially of the sexual organs. The prevalence of rickets is too general to warrant more than a suspicion that the disease may be associated with the status lymphaticus, and its presence can only serve as a warning that the two conditions sometimes co-exist, rendering the subject a dangerous one for administration of chloroform.

Of greater diagnostic importance is the discovery of a general or local hyperplasia of the superficial lymphatic structures. Enlargement of the faucial, lingual or pharyngeal tonsils, especially if accompanied by enlarged cervical, axillary or inguinal lymph glands, should at once arrest attention. The demonstration of well-marked lymphocytosis in some cases—a condition which may reasonably be expected to accompany general lymphatic hyperplasia—suggests that the examination of the blood may, in some cases, give a reliable indication of the presence of status lymphaticus. In view of the numerous deaths which have occurred during operations for simple goitre, and of the association of an enlarged thyroid with status lymphaticus, Blake (xliii.) urges that the safety of such operations should be more seriously considered. Before commencing the anæsthetic the thymus should be percussed out, and attention paid to the state of the lymphatic glands, the tonsils, and the back of the tongue. Cases of status lymphaticus have been reported, however, in which the spleen and tongue have been found normal, and no enlargement of the circumvallate papillæ has been seen. In 1909, the death of a young lady during a shampoo with carbon tetrachloride was reported in the papers,

and interest in the condition we are discussing was further aroused. Mr. Humphry, commenting upon the case in the *Lancet* of December 4th, 1909, takes the opportunity of giving the following details as of importance in diagnosis:—

1. Signs of a persistent thymus gland, as evidenced by lowering of the upper border of superficial cardiac dulness, in the absence of pulmonary emphysema or old tuberculous cavities at the lung bases, with or without fulness of the episternal notch. Too much attention should not be paid to a dull percussion note behind the sternum, as this region may sometimes be a little hyper-resonant.

2. A uniform prominence of all the tongue papillæ, especially of the circumvallate.

3. Symmetrical enlargement of the thyroid.

4. Distant and muffled heart sounds, associated with a soft, weak, and ill-sustained pulse which is often abnormally slow and inexcitable.

5. A variable amount of hyperplasia of any or all of the faucial, pharyngeal and lingual tonsils, also of the uvula, and the presence of adenoid growths. The liver and spleen may sometimes both be enlarged.

Mr. Humphry considers the co-existence of the conditions 1 and 2 to be pathognomonic of status lymphaticus.

TREATMENT.

By X-Rays.—In 1903 Heinecke (lxii.) published the results of his studies on the effects of X-rays on lymphoid tissue. He found that in young animals changes in the spleen occurred very promptly; there was a marked increase in pigment, disintegration of many cells, and reduction in size of the Malpighian corpuscles. It is noteworthy that these alterations occurred before any skin lesion; analogous changes occurred in very young animals in the thymus. He quotes the case of an infant, aged 5 weeks, who made a peculiar whistling noise during inspiration, and who suffered from some cyanosis. On percussion the thymus was 2 c.m. to the right and 3 c.m. to

the left of the sternal margin, merging into the cardiac dullness. The spleen was just palpable, and the cervical and inguinal glands were felt, being about the size of large peas. The child became worse, during three weeks' observation, and X-rays were applied through a window in a sheet of lead. The first application lasted one minute. These were increased to five minutes at the end of a week. In two weeks the dullness diminished and the stridor became less marked; there were about twelve exposures in all.

In view of the above case, it is interesting to note the pathological result of the action of the X-rays on the thymus which have recently been obtained by French observers, working on kittens (lxiii.). It was found that soon after radiation, the lymphocytes underwent changes, the nuclei retracted and lost their chromaffin structure; later they fragmented and became necrotic. Hassal's corpuscles increased very rapidly in size, became filled with coloured debris and with chromaffin remains. Later, these corpuscles became enormously enlarged, and their debris assumed a homogeneous and amorphous appearance. After repeated radiations, another change manifested itself. The thymus tissue was gradually changed, the destroyed lymphocytes were replaced by large epitheloid cells which toward the outer part of the gland became transformed into ordinary fusiform connective tissue cells.

By Operation.—This procedure is carried out in America and on the Continent more than in England. The thymus is either lifted up by sutures, which apply it more nearly to the sternum, or it is removed altogether. An account of such a case is supplied by Jackson (lxiv.). A boy aged 4 years had difficulty in breathing for six weeks, and a foreign body in his trachea was diagnosed. On performing tracheoscopy, a scabbard-shaped trachea was seen, the obstruction extending from the second to the fourth ribs. The X-rays showed the thymus to be enlarged. A long cannula was worn for four weeks, after which the thymus was excised at operation, and the cannula removed on the eighth day. This case would seem

to conclusively disprove Friedleben's dictum: "es giebt kein asthma thymicum." Similar cases are reported by Koenig (lxv.), Perrucke (lxvi.), Siegel (lxvii.) and Morfans (lxviii.).

Rehn (lxix.), at the German Surgical Congress, said that he had observed five cases of tracheal compression by the thymus. Two cases were operated upon, the mediastinum opened, and the gland drawn forward and stitched. These cases recovered. The remainder died. He considered that there was no doubt whatever as to the possibility of compression, and believed that radiographic evidence was of diagnostic importance.

Carter (lxx.), of New York, emphasises the following points in treatment:—

1. In all cases of laryngeal stridor it should be determined whether the thymus is or is not enlarged.

2. Surgical shock is badly borne by infants, and if the symptoms are not urgent, postural treatment should be tried. If relief is afforded by some position of head and neck, that position should be maintained by suitable apparatus until nature strengthens the trachea and enlarges the thorax. (The spontaneous cure of the results due to a simple enlarged thymus occurs in from six to twelve months and is due to an increased size of thorax and development of the tracheal rings.)

3. Intubation and tracheotomy do no good.

4. The surgical procedure adopted by Rehn should be performed at once, if there is danger of asphyxia.

The choice of anæsthetic is a subject which has given rise to great controversy. Deaths have occurred, not only under chloroform but also under mixtures, local anæsthetics and gas. The anæsthetic, however, is not always a predominant factor, though possibly a determining one. A case has recently been reported of a lad who died under chloroform, and in whom lesions consistent with status lymphaticus were found after death, but who had previously had nine or ten operations under chloroform with no harm.

Halsted (lxxi.) considers that, instead of being comparatively safe for children, chloroform should be especially feared during the period of childhood, because of the existence among so many children of the lymphatic diathesis, which is a positive contraindication to its use. For the removal of adenoids he considers that ether, properly administered, is incomparably safer than chloroform, and in a great majority of cases is the best anæsthetic for this operation. He quotes Kolisko (xxxv.), who had a great pathological experience, and who said, with reference to a small but definite number of deaths which occur every year from cardiac failure under chloroform, in whom no previous lesion of any organ was known to exist, that "in these cases we always find a condition of status lymphaticus."

In the *New York Medical News* of 1902, chloroform for children is condemned for the reason given above. The records of the Children's Clinic at Gratz for the twenty years prior to 1902, show that in every case of a fatality under chloroform the autopsy revealed the presence of status lymphaticus. There were no records of deaths under ether anæsthesia in patients of this type up to 1899 (lxxii.).

The proportion of deaths under chloroform to those under ether is greater during the first decade than during any other, and it is during the first decade that status lymphaticus is commonest. It may be that chloroform is held responsible for a majority of deaths in patients with this condition and its danger exaggerated because in Germany and Austria, where most of these cases are reported, chloroform is employed to the exclusion of ether.

McCardie (lxxiii.) has drawn attention to two features which are common in status lymphaticus, namely, nasopharyngeal obstruction and anæmia, factors which are intimately connected with the action of chloroform. Patients with the former require a long induction period, whereas anæmic people require very little, and the combination produces a subject to whom it is difficult and dangerous to administer chloroform.

Dudley Buxton (lxxiv.) in a discussion on this subject, put forward the theory that chloroform becomes locked in the chest owing to the expiratory obstruction, and absorption and poisoning occur the more readily, as the myocardium is feeble to commence with. It is probable that death is not due to a simple overdose, as many cases have been reported in which the corneal reflexes were present when death occurred. Such a case occurred at Guy's Hospital in the writer's experience. Two or three drops of chloroform had been applied on lint to a small child with phimosis, when the pulse suddenly failed without warning. The operation was abandoned and the child was brought round, to the surprise of all, with stimulants. Shortly afterwards convulsions developed, probably from the strychnine which was used in large doses, and after some twelve hours the child died. At autopsy the only abnormality found was a fairly typical condition of status lymphaticus. With reference to syncope, Embley and Martin have shown that, whereas vagal inhibition is prevented by a certain amount of chloroform in the blood, a larger percentage has no effect upon this. May not a patient with the smaller percentage of chloroform, and suffering from status lymphaticus, fail to escape this inhibition?

Hewitt (lxxv.) considers it highly probable that the cases of supposed primary heart failure under anaesthetics have been misinterpreted. According to him the evidence connecting status lymphaticus with death under chloroform narcosis is not convincing, but patients are certainly liable to embarrassment of breathing of an obstructive nature. Fatalities from status lymphaticus, associated with the use of local anaesthetics, have not been commonly reported in this country.

The following two cases are found in the Continental literature. In the first, a woman of 30 was operated on for a cyst in her neck. After first laughing at her fears, she suddenly became pallid, and respiration stopped. At autopsy a typical condition of lymphatism was found (lxxvi.). The second case is that of a woman of 31, suffering from Graves' disease,

who died fifteen minutes after an operation for removal of her thyroid gland (lxxvii.). The post-mortem showed a very thick thymus associated with enormous hyperplasia of the whole lymphatic apparatus.

Dr. Levy communicated to the recent meeting of the Royal Society of Medicine experiments he had performed bearing on the possible relation of thymus secretion to sudden death under chloroform. He injected a fresh extract of sheep's thymus into the peritoneal cavity and subcutaneous tissues of cats, while they were under chloroform. Beyond a slight fall of blood pressure there was no unusual reaction to the anaesthetic, and stimulation of the central and peripheral ends of the cut vagus nerve did not produce any greater effect, direct or reflex, after the injection than before. He also found no difference in the induction period of anaesthesia, after feeding animals with fresh thymus gland and with commercial dried extract of the gland. His experiments failed to afford any evidence that the contents of the hypothetical secretion of the thymus were operative in the production of syncope under chloroform anaesthesia.

INCIDENCE OF THE DISEASE AND MANNER OF DEATH.

The majority of reported cases have died as a result of chloroform narcosis, but death has occurred in a great many other ways, and it is noteworthy that in most of these the immediate cause of death was quite inadequate to cause a fatal termination in a healthy person. Nordmann and Paltauf refer to seven cases of death in persons who fell into the water; in none of these were the ordinary signs of drowning to be found, but the usual evidence of status lymphaticus was present. In infants death may occur during sleep and be attributed to overlying, and it is essential therefore to recollect that status lymphaticus may be the true cause of death in medico-legal autopsies upon such cases. An enlarged thymus, again, may be an obstacle to the establishment of respiration in the newly born. It is difficult to find any observations on the racial occurrence of status lymphaticus. Of Blake's seven

recorded below, three were negroes. The association of status lymphaticus with rickets, and the frequency of rickets in negro races, is suggestive in this connection.

Appended are notes of a number of cases in which death has been ascribed to status lymphaticus. Some occurred in the practice of the writer, but they are mostly gathered at random from the pages of contemporary literature.

Whether or no the reader, from a perusal of this paper, carries away a conviction that more than a few persons die as a direct result of what has come to be known as status lymphaticus, he will assuredly, on weighing the evidence, be compelled to agree that the condition means more than some would have us believe, to whom status lymphaticus means but a cause for an otherwise unexplained death.

From the foregoing remarks he will probably also agree that much darkness still exists which the light of knowledge has yet to penetrate.

The following are brief notes of 61 cases, recorded and unrecorded:—

CASE 1.—F., aged 5 years. Death during trivial operation. Chloroform twenty minutes. Pulse failed before respiration. Post-mortem, thymus 7 by 5 by 2 c.m.; tonsils, spleen, and Malpighian bodies enlarged. Peyer's patches enormously enlarged, resembling polypoid outgrowths. Death from asphyxia (dark colour and fluidity of blood; general venous congestion of viscera; subpericardial and subpleural hæmorrhages); no evidence of rickets. (Ewing, *New York Medical Journal*, July, 1897.)

CASE 2.—F., aged 27 years. Death following gynæcological operation. Post-mortem, old rickets, hypoplasia of heart and aorta, thymus persistent.

CASE 3.—M., aged 18 months. Died while having tea. Thymus $1\frac{1}{4}$ ounces, $3\frac{1}{2}$ inches long: dyspnoic attacks since birth; tonsils and adenoids enlarged; spleen of same weight as thymus; no signs of rickets. (Rooth, *British Medical Journal*, 1906, p. 737.)

CASE 4.—M., aged 7 weeks. Found dead in bed. Thymus weighed 1 ounce; no signs of tracheal compression; nothing abnormal observed during life. Punctiform hæmorrhages on thymus and ventricles of heart. (Anderson-Smith, *British Medical Journal*, 1907, p. 1536.)

CASE 5.— .. aged 8 months. Died in bed. Thymus extended from thyroid to diaphragm; weight 2 ounces; 4 by $2\frac{3}{4}$ inches. Trachea not compressed; accustomed to throw its head back. (Jessop, *British Medical Journal*, 1905, p. 1586.)

CASE 6.—M., aged 3 months. Operation for phimosi; chloroform. Puke failed before respiration; thymus weighed 31 grms.; Peyer's patches enlarged, glands not enlarged. This child, as recorded above, recovered with strychnine from its collapse, but died later from convulsions; the original collapse was considered to be due to status lymphaticus.

CASE 7.—M., aged 7 months. Died during chloroform for operation on phimosi and tonsils and adenoids. Thymus 2 by 3 inches; rickety; spleen dark and congested; great venous engorgement. (Simmon, *New York Medical Journal*, August, 1904.)

CASE 8.—M., aged 21. Operation under chloroform and C.E. mixture; died suddenly; thymus 24 grms.; thyroid and mesenteric glands enlarged; spleen, Peyer's patches and follicles much enlarged; heart fatty. Patient was neurotic and suffered from faintness. (Hilliard, *British Medical Journal*, January, 1908.)

CASE 9.—F., aged 18. Died during operation under gas and chloroform. Cretin; great cyanosis while "going under"; thymus large; thyroid absent. (Owen, *British Medical Journal*, 1904, p. 1635.)

CASE 10.—M., aged 17 years. Found unconscious. Thymus 19 grms.; spleen enlarged; heart and aorta hypoplastic; multiple hæmorrhages in lungs.

CASE 11.—M., aged 18 years. Found unconscious. Thymus enlarged; urine albuminous, spleen and lymphatic glands enlarged.

CASE 12.—M., aged 23 years. Found unconscious. Thymus enlarged; spleen big and lingual follicles prominent. (Cases 10, 11 and 12, Lamb, *Wiener Klinische Woch.*, 1899, p. 44, who considers certain cases of coma may be due to status lymphaticus.)

CASE 13.—F., aged 20 years. Died during operation for adenoids. Thymus much enlarged. Throat reflex present at time of death.

CASE 14.—F., aged 94 years. Persistence of thymus. (Claude, *Bull. Anat. Soc., Berl.*, 1897, p. 210.)

CASE 15.— .., aged 6 weeks. Died in bed. Thymus 6 by 5 by 2 c.m.; death from asphyxia. (*Edinburgh Medical Journal*, N.S., 1899, v.)

CASE 16.—F., aged 29 years. Died in Guy's Hospital during operation for exophthalmic goitre. Thymus weighed 98 grms. (*Lancet*, 1907, p. 1103.)

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CASE 17.—M., aged 17 years. Death under c. and e. Thymus $1\frac{1}{2}$ ounces, spleen $6\frac{1}{2}$ ounces, and larger than normal. Malpighian bodies and mesenteric glands enlarged; patient anæmic and poorly nourished. (*Lancet*, 1907, p. 1759.)

CASE 18.—M., aged 7 months. Sudden death. Thymus enlarged.

CASE 19.—M., aged $1\frac{3}{4}$ years. Sudden death. Thymus enlarged; evidence of rickets. (Cases 18 and 19, Peacocke. *Dublin Journal of Medical Science*, 1903, p. 116.)

CASE 20.—F., aged 1 year. Died after taking soothing syrup containing morphia one-twelfth grn. Status lymphaticus found. (MacTaggart, *Montreal Medical Journal*, 1903, p. 327.)

CASE 21.—M., aged 6 years. Found unconscious. Thymus big and pressing upon aorta and great vessels; marked cyanosis; no hæmorrhage found. (Dixon, *Australasian Medical Gazette*, 1898, p. 17.)

CASE 22.—., aged 10 weeks. Sudden death during apparent health. Thymus $\frac{3}{4}$ ounce. (*Archives of Pediatrics*, xii., p. 109.)

CASE 23.—F., aged 2 months. Sudden death; cough and asphyxia. Thymus 31 grms., 8 c.m. long; found to compress trachea. (Morfan, *Bull. Med.*, 1894, p. 495.)

CASE 24.—., aged $3\frac{1}{2}$ months. Death sudden; pallor and throwing back of head were marked. Thymus 7 by $3\frac{1}{2}$ by 2 c.m., rickety; thymus covered pericardium; spleen enlarged; bronchial, mesenteric and inguinal glands much enlarged. (Jones, *Archives of Pediatrics*, 1903, xx., p. 5967.)

CASE 25.—F., aged 11 months. Fell off stool and died. Asthma and "seizures" had been noticed previously.

CASE 26.—M., aged 22 months. Convulsions and death during influenza. Thymus 52 grms., 10 by 9 by 2 c.m.; no tracheal compression. Hassall's corpuscles numerous and degenerated; Malpighian bodies very large; spleen and lymphatic glands much enlarged. (Cases 25 and 26 Biechele. *Archives of Pediatrics*, 1904, p. 21.)

CASE 27.—M., aged 6 years. Death 10 hours after chloroform, for slight operation. High temperature and delirium; superficial symptoms of status lymphaticus, e.g., fine silky hair and fair complexion; tonsils and adenoids large, and superficial lymphatic glands enlarged. (Gwyer, *Annals of Surgery*, 1904, p. 39.)

CASE 28.—M., a few weeks old. Unconsciousness; crowing inspiration; thorax arrested during inspiration; glottis closed. Inspiratory shriek ushered in respiration after thirty seconds' interval, completing marked attack of laryngismus stridulus; repeated attacks before death. Thymus $5\frac{1}{2}$ by 4 by 2 c.m.; dull note over manubrium. Child weighed $6\frac{1}{4}$ lbs. at birth. (Happel, *Albany Medical Annals*, 24, p. 8.)

CASE 29.—., aged 7 months. Turned suddenly blue in cradle, had a fit and died; well nourished, weight 11 lbs. Thymus weighed $\frac{3}{4}$ ounce; no pressure on trachea; many adenoids; tonsils not enlarged; mesenteric glands enlarged and resembling bunches of grapes. Peyer's patches much hypertrophied; thyroid normal. No superficial lymphatic hyperplasia; heart normal; no rickets; venous engorgement general. Lymphoid elements of thymus and mesenteric glands found microscopically to be hypertrophied. (Walker, *Lancet*, 18th December, 1909.)

CASE 30.—M., aged 9 years. Injury to knee; operation; death shortly afterwards. Thymus 12 by $4\frac{1}{2}$ by 3 c.m.; usual signs of status lymphaticus; aorta small. (Richardson, *Boston Medical and Surgical Journal*, 1905, p. 280.)

CASE 31.—F., aged 10 years. Death occurred under chloroform, before the operation. Post-mortem, nothing abnormal found except considerable enlargement of mediastinal and mesenteric glands. (*British Medical Journal*, 1896, p. 859.)

CASE 32.—M., aged 20 years. Sudden unconsciousness; death in twenty-four hours. Thymus size of apple; hyperæmia of all organs; genitals well developed; adrenals very small, especially medullary portions; hyperplasia of lymph nodes in tongue and neck; medulla of thymus hyperplastic; no chromaffin masses among large abdominal plexus; but few chromaffin cells in rest of sympathetic nervous system. Wiesel, who reports this and the next three cases, says, "So I consider myself justified in believing that in this case a congenital hypoplasia of the chromaffin system was coincident with status lymphaticus." (*International Clinics*, 15th series, vol. 2.)

CASE 33.—M., aged 40 years. Died from accident. Thymus the size of a fist; hyperplasia of glands in neck and tongue; adrenals small; hypoplasia of chromaffin system.

CASE 34.—M., aged 15 years. Died with clinical symptoms of Addison's disease. Thymus persistent; adrenals small, with very narrow medulla; hypoplasia of chromaffin system.

CASE 35.—F., aged 20 years. Consumptive; adrenals very small; hypoplasia of chromaffin system, also of vascular system and genitals; aorta barely admitted a little finger.

CASE 36.—F., aged 21 years. Died while eating a pear; subject of Graves' disease, but was improving rapidly under treatment. Thymus very large, and equal to thyroid in size. Death ascribed to some obscure nervous influence. (Codd, *British Medical Journal*, 1896, p. 19.)

CASE 37.—M., aged 11 months. Sudden death in Guy's Hospital, 1908; had been treated for laryngeal stridor; slight stridor in hospital; death apparently from syncope; no dyspnoea; slightly rickety. Post-mortem,

34 *The Thymus Gland and the Status Lymphaticus.*

thymus 33 grms.; size of a tangerine orange. Bronchial, salivary and mesenteric glands enlarged. Intestinal follicles very prominent; spleen weighed 100 grms. (P. M., No. 38.)

CASE 38.—New born. Sudden death; child weighed 6½ lbs.; thymus 3½ by 3 by 1 inches; trachea probably compressed when head was thrown back. (Dolinsky, *Annal de Gyne. et d'Obstet.*, May, 1896.)

CASE 39.—New born. Sudden death. Thymus hypertrophic with small hæmorrhagic areas.

CASE 40.—New born. Died suddenly. Thymus hypertrophic; cirrhosis; gastro-intestinal trouble. (Cases 39 and 40, *Durante, Semaine Med. Meh.*, 18, 1896.)

CASE 41.—M., aged 8 months. Sudden death. Thymus 28 grms.; each lobe 2½ inches long; no previous illness. Trachea nearly encircled by thymus; all the lymphatic glands much enlarged, except inguinal and cervical; no caseation. (Stewart Smith, *Lancet*, 7th November, 1908.)

CASE 42.—F., aged 8 years. Death under chloroform for tonsils and adenoids; laryngismus stridulus three years before. Thymus 22½ grms.; 12 c.m. long; no compression; glands and follicles very large; aorta normal; tongue large; thyroid normal; no history of fits or rickets.

CASE 43.—F., aged 13 years. Death under chloroform for tonsils and adenoids. Thymus 25¼ grms.; thyroid very large, weighing 38½ ounces; enlargement of glands and follicles.

CASE 44.—F., aged 17 years. Chloroform for goitre operation. Thymus 28 grms.; trachea very narrow; tonsils, tongue, follicles and Peyer's patches enlarged; general lymphatic enlargement.

CASE 45.—M., aged 20 years. Death under chloroform. Thymus not abnormal; general lymphatic enlargement; tonsils and tongue large.

CASE 46.—F., aged 6 years. Death under chloroform for tonsils and adenoids. Thymus 17 grms.; usual signs.

CASE 47.—M., aged 8 months. Operation for phimosis; death shortly afterwards. Thymus weighed 2½ ounces; size of child's lung, practically filling upper third of thorax; signs of rickets; spleen large; abdominal and bronchial glands not enlarged.

CASE 48.—F., aged 6 months. Died three days after operation for adenoids; history of fits; rickets. Thymus 2 by 1 inches; thyroid normal; tonsils small, otherwise a general glandular enlargement. (Cases 42—48, *McCardie, British Medical Journal*, 1908, p. 196.)

CASE 49.—M., aged 5½ years. Death after three days' illness; previous good health; breathing noisy; vocal cords moved well; diagnosis made of enlarged lymphatic glands; symptoms toxic, and not due to any

pressure. Some want of resonance over sternum. Thymus $\frac{1}{2}$ ounce; eosinophile leucocytes in large numbers; Hassal's corpuscles numerous and large; mesenteric glands and splenic corpuscles large. (Sidney Phillips, *Clinical Journal*, 12th February, 1908.)

CASE 50.—F., adult. Died of fright while pursued by her husband. Thymus found to be $1\frac{1}{2}$ ounces; 2 inches in width. (*Times*, 19th November, 1908.)

CASE 51.—M., aged 3 months. Sudden death. Thymus bulky and heavy, 15 grms. Peyer's patches and solitary follicles much enlarged; subpleural and subpericardial hæmorrhages.

CASE 52.—M., aged 13 months. Sudden death. Thymus 16 grms.; signs as above; heart dilated.

CASE 53.—M., aged 4 months. Sudden death. Thymus 30 grms. Peyer's patches and solitary follicles enlarged.

CASE 54.—F., aged 5 months. Thymus 34 grms.; tonsils and spleen not enlarged. (Cases 51—54, Thursfield, *St. Bartholomew's Reports*, vol. 38, 1902, p. 129; only one of these cases was rickety; a history of its was found in three cases.)

CASE 55.—M., aged 27 years. Death during operation on thyroid. Thymus weighed 135 grms.; 16 by 11 by $1\frac{1}{2}$ c.m.; general lymphatic hyperplasia; recurrent nerves not affected.

CASE 56.—M., aged $2\frac{1}{2}$ years. Death after operation for phimosi. Thymus 53 grms.; $8\frac{1}{2}$ by $5\frac{1}{2}$ by 2 c.m.; no tracheal compression; axillary and inguinal glands palpable. Peyer's patches and Malpighian bodies enlarged. Cultures from viscera sterile.

CASE 57.—F., aged 32 years. Negress. Died during hysterectomy. Thymus 46 grms.; usual appearances.

CASE 58.—M., aged 55 years. Death before commencement of operation. Thymus weighed 22 grms.

CASE 59.—M., aged 40 years. Negro. Admitted for unconsciousness and dyspnoea; dullness over manubrium sterni and to left. Post-mortem month later; aortic aneurysm found presenting no obvious reason to cause death. Thymus 49 grms. General lymphatic hyperplasia.

CASE 60.—M., aged 30 years. Sudden syncope. Thymus 35 grms.

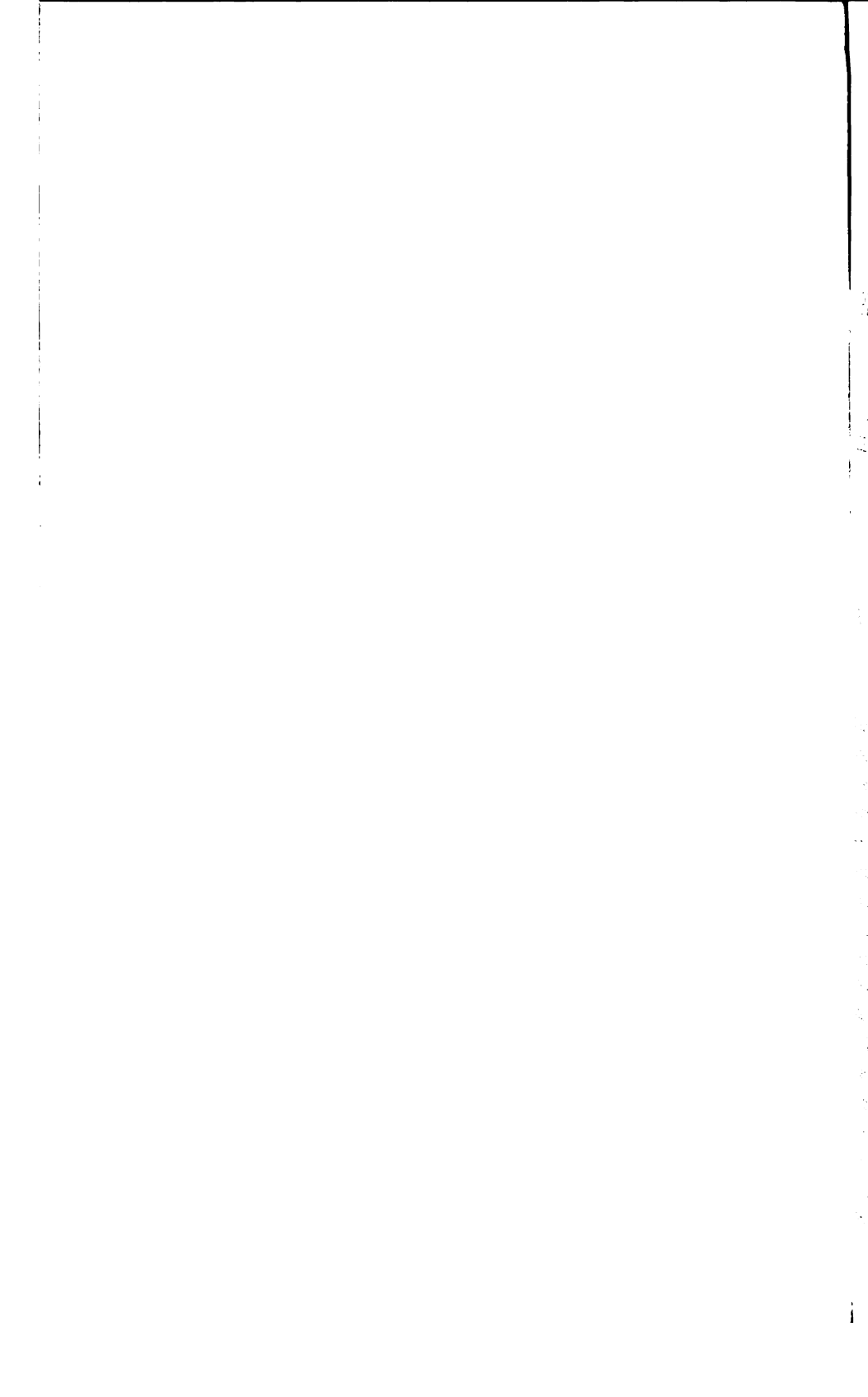
CASE 61.—F., aged 30 years. Death after a normal labour. Thymus 32 grms. (Cases 55—61, Blake, *Annals of Surgery*, 1902, p. 35, who points out that none of his cases are explainable on the mechanical theory, which fact, in his view, supports that of a toxæmia. It is notable that 6 of his 7 cases are adults.)

Wynn has published accounts of 21 fatal cases with typical signs of lymphatism. Thymus varied from 17—35 grms., the average being 24 grms.; 8 cases died under chloroform; 6 died after injuries which would not usually cause sudden death. (*B.M.J.*, 1908, p. 352.)

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PRIMARY UNILATERAL RENAL TUBERCULOSIS.

A REPORT UPON 13 CASES, WITH A
COLLECTION OF 79 CASES FROM THE RECORDS OF
GUY'S AND St. PETER'S HOSPITALS.

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THE subject of tuberculosis of the genito-urinary tract has attracted considerable attention during recent years, and the data derived from the collected cases have shown that many ideas formerly held have of necessity to be given up as untenable. The close association of the genital and urinary organs in the male, and the spread of tuberculosis from one to the other, are now better understood, and it has been shown that tuberculous disease may descend from the kidney to the bladder and genital annexa, or, commencing primarily in the epididymis, may spread by the vas deferens to the seminal vesicle, prostate and bladder and subsequently ascend to the kidney *via* the ureter. It was at one time doubted whether tuberculous disease in the genito-urinary tract existed as a primary disease or as secondary to some other lesion elsewhere in the body, such as the lungs or the skeleton, but Walker found the disease to occur as a primary invasion in 52 out of 174 cases in which the genito-urinary organs were affected with tuberculosis.

With regard to the urinary organs apart from the generative system, very opposite opinions have been held regarding the primary origin of the disease; it has been stated by some that the bladder is rarely, if ever, the first part affected, whilst others have maintained that the bladder is usually the earliest organ involved. Undoubtedly the bladder may be involved primarily, but it is much more common to find the commencement of the disease in the kidney. It is stated by Walker that in a series of 279 cases of genito-urinary tuberculosis the kidney was the first organ involved in 184, and the epididymis in 80, whilst the fact that tuberculous foci may be found in the kidney only, or, if the infection has spread, that the older process is found in the kidney, tend to show that the latter is primarily affected. Halle and Motz state that in a series of 100 cases of urinary tuberculosis they found a number in which the infection was present in the kidney, renal pelvis and ureter, where the bladder was free from disease, but that they found no instance in which the ureter and renal pelvis were involved without infection of the corresponding kidney.

Renal Tuberculosis occurs in the following forms:—

1. Acute miliary tuberculosis.
2. Subacute diffuse tuberculosis.
3. Chronic caseous tuberculosis.

The acute miliary tuberculosis of the kidney occurs as a part of a general miliary tuberculosis, usually in children, and is, in the great majority of cases, bilateral.

The subacute diffuse tuberculosis is found in association with tuberculous lesions elsewhere in the body, occurring in the later stages of the disease. It is usually bilateral, each kidney containing numerous caseating and purulent foci, and is most frequently found in children.

The chronic caseous form of tuberculosis frequently occurs as a primary disease in one kidney. It commences as a localised deposit in the renal tissue, gradually enlarging and caseating. Usually several foci are present in various stages

of development, some solid, others caseous, whilst the older cavities break down and coalesce. Ultimately a cavity opens into the renal pelvis, when the lining membrane of the latter and of the ureter become studded with tubercles.

The disease commences primarily in one kidney, and may exist for a long time before the other organ is affected. It was formerly held that the disease was more frequently bilateral, this opinion being based upon the evidence obtained from post-mortem examinations at the termination of the disease, but even here it must be noted that the process is much more advanced on one side than on the other. The results obtained in recent years by operation upon the diseased side in the earlier stages, however, show that the disease is at first, at all events, unilateral in origin. Of this caseous form of unilateral renal tuberculosis, I have had under my own notice thirteen cases, in eleven of which nephrectomy has been performed, and I have, by the kind permission of the medical staffs of Guy's and St. Peter's Hospitals, collected 79 cases of the disease amongst the records of the last ten years. In collecting these cases I have carefully excluded all those in which there was any reason to doubt that the disease was primarily renal in origin, and have also excluded from the list cases which were considered of a doubtful nature. In 47 of these cases, operations were performed on the diseased kidney. It is upon this collection of 92 cases that I have based this article.

Pathological Anatomy.—The various descriptions which have been given to a tuberculous kidney depend partly upon the duration and extent of the disease and partly upon the mode of invasion of the organ. Leaving out of consideration the miliary form of tuberculosis and the secondary infection of the kidney from tuberculous disease of the lower genito-urinary passages, the anatomy of the diseased organ will be found to vary with the extent of the disease. Commencing in nearly all cases by the deposition of the tubercle bacillus in the kidney from the blood stream, there is a localised proliferation of connective tissue and epithelial cells, with the blockage

of a small vessel, to form the typical miliary tubercle, appearing to the naked eye as a small greyish nodule in the renal tissue. These tubercles are usually multiple, gradually enlarge and coalesce to form a yellow mass of varying size, surrounded by an area of nephritis. These masses commonly commence at one or other pole of the kidney, and may slowly caseate to form a putty-like mass in the kidney, or may soften to form a tuberculous abscess. Gradually extending, one of these cavities may ultimately open by ulceration into the renal pelvis, discharging its contents into the urine and at the same time promoting infection of the lining membrane of the renal pelvis and ureter. The mucous membrane of these passages becomes studded with tubercles, thickened by submucous infiltration, and the ureter is rendered rigid and at the same time shortened in its length, so that the vesical end of the ureter becomes drawn upwards and outwards from its normal position at the bladder base. Later, the vesical mucous membrane in the immediate vicinity of the ureteric orifice and covering the terminal portion of the ureter becomes infected, appearing at first as a submucous infiltration, but ultimately showing the typical deposition of tubercle. This vesical infection ultimately spreads over the surface of the bladder, and may attack the other ureter or spread to the neighbouring genital organs.

The progress of the disease varies considerably. In some cases the caseous masses in the kidney enlarge very slowly and become surrounded by fibroid changes, so that the organ may present several rounded bosses which, on section, are found to be formed of yellow putty-like material separated by sclerosed renal tissue; to this form the name of "massive tuberculous degeneration" has been given. In this way the renal tissue may be entirely replaced by thick caseous material, and there is preserved in the museum of St. Peter's Hospital a specimen of advanced urinary tuberculosis in which the right kidney, the primary seat of the disease, is entirely converted into a mere shell tightly packed with thick cheesy substance. During the disease the ureter may become partially obstructed by the

mucous and submucous infiltration, or by the impaction of tuberculous debris from the renal cavity, so that the kidney enlarges to form a distinct tumour. Further, the damaged kidney is particularly prone to become infected with other infective organisms, so that should there be any cystitis or suppuration in any other organ, the tuberculous kidney may be readily infected with pyogenic organisms, when the disease runs a much more rapid course. The tuberculous masses break down to form localised abscesses, which may coalesce or open into the renal pelvis, or which may enlarge to form a tuberculous pyonephrosis. In some cases the process extends to the perinephric tissues, and in 4 cases from the 92 collected, a tuberculous perinephric abscess was present in association with a tuberculous kidney.

Age, Sex, and Relative Frequency with which each Kidney is Infected.

Age.—In an analysis of 373 cases, Walker found that the largest number of cases of unilateral renal tuberculosis occurred between the ages of twenty to thirty years. In this collection of 92 cases, the ages of 89 in which it was mentioned were as follows:—

Between 1 and 10 years	...	4 cases
„ 11 „ 20 „	...	12 „
„ 21 „ 30 „	...	29 „
„ 31 „ 40 „	...	32 „
„ 41 „ 50 „	...	8 „
„ 51 „ 60 „	...	4 „

so that 61, or over 68 per cent., occurred between the ages of 21 and 40 years.

Sex.—In the same series the disease occurred in 49 males and in 43 females.

Frequency of each side.—In 91 cases in which the side of the disease is noted, it occurred on the right in 48 cases and on the left in 43 cases.

The Symptoms of Unilateral Renal Tuberculosis.—The symptoms of renal tuberculosis are at first little marked, and the

disease may reach a somewhat advanced stage before the patient seeks advice, and even then they are often misleading. The occurrence of tuberculous nodules in the kidney may cause a slight aching pain in the loin, but, as a rule, no symptoms are produced until a renal calyx becomes involved in the disease, and a tuberculous focus opens into the renal pelvis. In one of my cases (Father D. M.), the patient had been rejected for life insurance on account of albuminuria eighteen months before any symptom of urinary tuberculosis became manifest; possibly this was caused by the surrounding zone of nephritis around a tuberculous deposit.

The symptoms of renal tuberculosis may be local or general. The local symptoms include lumbar pain, frequency of micturition, painful micturition, pyuria and hæmaturia, together with renal enlargement, thickening of the ureter and the presence of the tubercle bacillus in the urine. I have endeavoured to ascertain the initial symptom which first attracted the patient's attention, and I found in the thirteen cases under my own care that the most common symptom was increased frequency of micturition and lumbar aching, whilst from the 79 cases from the hospital records 17 cases commenced their symptoms with increased frequency of micturition alone, whilst 4 were with the association of increased frequency of micturition with lumbar pain. In 25 cases the symptoms commenced with aching in the lumbar region, whereas in 13 cases the first symptom noticed was an attack of renal colic. In 11 cases the first symptom was hæmaturia unaccompanied by pain, whilst in two others the initial symptom was a tumour in the loin, in one of which there was a large tuberculous pyonephrosis, whilst the other proved to be a tuberculous perinephric abscess in association with renal tuberculosis. In five cases the initial symptom was stated to be turbidity of the urine.

Pain.—Aching in the loin is one of the earliest symptoms complained of by the patient. The aching is of moderate intensity and is not aggravated by movement. This slight constant aching may be present alone for some time, but as

the disease progresses it becomes gradually increased to a dull "heavy" or "dragging" pain in the back. It is commonly felt in the renal angle posteriorly and in the subcostal region in front, but occasionally is present also in the iliac fossa. This renal aching is occasionally felt on the other than the diseased side, and in a case under my care the pain was felt on both sides when one side only was affected. Apart from the constant lumbar aching, there may be acute attacks of pain exactly resembling the renal colic during the passage of a calculus. These attacks are caused by the passage or partial occlusion of the ureter by caseous tuberculous debris from the renal focus, and are accompanied by faintness, vomiting and sweating. These acute attacks of colic may cease suddenly by the passage of the caseous mass into the bladder, when it may be found in the urine on micturition.

In the 92 cases collected, lumbar aching was stated to be present in 84, was absent in 6, and not mentioned in 2 cases. In the same series, 32 cases had at some time during their illness an attack or attacks of renal colic; 36 cases are specifically noted as having had no attack of colic, whilst in the remaining 24 no mention of colic is made.

Increased Frequency of Micturition is a common and early symptom of renal tuberculosis, and may for a time be the only symptom present. The increased frequency is present during both the day and the night, and may be marked before there is any infection of the bladder or lower ureter. In several cases of renal tuberculosis, I have found the bladder to be quite healthy and capable of a distension of twelve to fifteen ounces without anæsthesia, whilst the desire to micturate has been present every hour. In one case in which a complete renal fistula has been established by a previous nephrotomy, there was no increased frequency of micturition.

This symptom may be due to ureteric infection, or, in later cases, to descending infection of the bladder, or to the accumulation of caseous muco-purulent debris in the bladder. With the gradual progress of the disease the ureter becomes infected

with descending tuberculosis, and the close anatomical relationship between the lower end of the ureter and the bladder may in part account for the symptom. With the shortening of the ureter by infiltration, the portion of the bladder around the ureteric orifice becomes drawn up, and at the same time the vesical mucous membrane becomes congested and œdematous, both around the orifice and in the portion of the bladder immediately over the lower end of the ureter. This congestion is at first of inflammatory origin, though later will be found to contain distinct tuberculous nodules. Thus, when the disease has reached the lower end of the ureter, increased frequency of micturition will be present from the inflammatory processes in immediate proximity to the vesical wall, in similar manner to the increased frequency of micturition noted in cases of calculus impacted in the terminal portion of the ureter.

In the 92 cases collected increased frequency of micturition was stated to be present when the patient came under observation in 77 cases, or nearly 84 per cent., was not present in 7 cases, and was not mentioned in 8 cases. In 41 cases which were subjected to cystoscopic examination, the bladder was found quite normal in 9, the ureteric orifice of the affected side was found retracted or congested in 17, whilst in 15 cases there is mention of the presence of early tuberculosis of the bladder either as a ring of submucous tubercles around the orifice of the ureter, or as a small ulceration in some part of the vesical wall.

Alteration in the Urine.—The urine is pale and of low specific gravity, and from the first is usually increased in quantity. Later, it becomes opalescent and clouded, and contains both pus and blood from the ulceration of a renal focus. The reaction is nearly always acid, unless a secondary pyogenic infection be added to the primary disease, when it becomes alkaline. The appearance of the urine may show marked changes dependent upon the occlusion of the ureter by tuberculous masses. Thus, if the duct be wholly blocked the urine may, during that period, be clear, but will again become purulent and turbid when the obstruction is removed.

Pyuria.—In the earliest stages, whilst the disease is limited to the caseous areas in the kidney, the urine will be free from pus, but when the tuberculous process reaches a calyx, pyuria will occur. The amount of pus present in the urine may vary from time to time from occlusion of the ureter, or may be increased from the emptying of an additional focus into the renal pelvis.

In 92 cases pyuria was present in 87 when first the patient came under observation. In a large number of these the patient gave a history of turbidity of the urine, but in the remainder the pus was found present on microscopical examination of the urine. In three cases there is no mention of the presence or absence of pus in the urine, and in two it is stated to be absent. In one of these a complete renal fistula existed on the diseased side, so that the urine collected from the bladder was that excreted by the healthy kidney, whilst in the other the kidney was almost entirely caseous and functionless and surrounded by a perinephric abscess.

Hamaturia.—Occasionally the first symptom of renal tuberculosis is hæmaturia, but it is seldom severe or associated with attacks of increased pain as in renal stone. The blood may be present in the urine enough to cause a distinct red coloration for a few days and then be absent for some time. It is intimately mixed with the urine, usually associated with pyuria, and is not influenced by exercise. Occasionally the ulceration of a calyx may cause a smart hæmaturia with the passage of tapering clots from the ureter, but this is exceptional. In the majority of cases blood discs will be found in the urine on microscopic examination. In the later stages, when there is in addition to the primary renal tuberculosis a descending infection of the bladder, blood may be present in the urine, but the character of the hæmaturia changes, and it will be found that the blood is not mixed with the urine throughout micturition, but that the final few drops of urine are tinged with blood.

In the 92 cases forming the basis of this paper I have made particular note of the occurrence of hæmaturia. I find that in 54 cases it is definitely stated by the patient that blood was present in the urine during some part of the illness before coming under observation, so that there must have been sufficient blood in each of these cases to have stained the urine enough for the patient to notice it. In 20 cases it is stated that hæmaturia had not been present, but in some of these blood was found in the urine on microscopical examination. In the remaining 18 cases there is no mention of hæmaturia in the report. In 15 cases out of the 92 hæmaturia was the initial symptom noticed by the patient, the amount of blood being "profuse" in five cases and "slight" in ten.

In ten instances the hæmaturia was stated to have been excessive, in five of which a profuse hæmaturia was the first symptom of the illness, whilst in the remaining five cases an attack of profuse hæmaturia occurred after the onset of other symptoms. The term "profuse" must at any time be used in a relative sense, and in only one case of the thirteen under my own care could this term be applied; in this case the urine was of a bright red colour from the contained blood. Hæmaturia, then, is a common symptom of renal tuberculosis, usually slight in amount and often marked by remissions. Profuse hæmaturia is uncommon.

Albuminuria is a constant symptom when once the renal focus has discharged into the pelvis of the kidney. It is possible that albuminuria might be found present were the urine from a tuberculous kidney examined before ulceration had occurred, arising from the area of nephritis surrounding a tuberculous focus. In one case under my care (D. M., case 4) the patient had been refused for life insurance on account of albuminuria eighteen months before he noticed his first symptom of renal disease. He made a rapid recovery after removal of the diseased kidney, and remains well after a period of over four years. The remaining kidney shows no signs

of nephritis, and I am inclined to look upon this early albuminuria as due to nephritis around the tuberculous focus in the diseased organ.

The Presence of Tubercle Bacillus in the Urine is a most important sign of tuberculous disease in the urinary tract. It may be necessary to make a prolonged search for them and, if unsuccessful in a suspected case, inoculation experiments should be carried out. The absence of tubercle bacilli from the urine should not be allowed to alter the diagnosis, but rather suggest another search. In one case under my care tubercle bacilli were only found in the urine after a thorough search by an expert in the sixth specimen submitted to him, and it is a significant fact that in this case no blood was at any time found present in the urine. It was long ago pointed out to me that the most favourable time for finding tubercle bacilli in the urine was just after an attack of hæmaturia, and both in renal and vesical tuberculosis this holds good. In 64 cases in which mention of examination for tubercle bacilli in the urine is made they were found present in 43 cases.

Dysuria.—In an uncomplicated case of renal tuberculosis there is no pain during or after micturition, but when the lower end of the ureter or bladder becomes infected, the patient complains of a smarting pain in the glans penis after micturition. This pain may be present before there is any actual tuberculous infiltration of the bladder base from the presence of infection at the terminal portion of the ureter or to the inflammatory congestion of the submucous and mucous tissues of the bladder in the situation of the ureteric orifice of the diseased side. It should be noted that this symptom differs from that of increased frequency of micturition in that it is caused by an inflammatory condition of the lower ureter or bladder, whereas increased frequency may be present when the disease remains localised in the kidney.

Objective Symptoms.—Tumour of the Kidney.—In most cases of tuberculous disease of the kidney the organ becomes palpable and may be felt to be enlarged unevenly or to present rounded

prominences. Occasionally with renal distension from ureteric obstruction, the kidney becomes pyonephrotic, assuming a rounded shape, and may form a visible prominence in the ilio-costal space. In other cases, again, a distinct mass may be felt in the loin which feels clinically like an enlarged kidney, but yet on exploration proves to be an inflammatory infiltration of the perinephric tissues around a tuberculous kidney; in some cases a tuberculous perinephric abscess may be present. Commonly the kidney is felt to be enlarged on bimanual examination, to be slightly irregular, and to be tender on pressure. Care must be taken, however, not to mistake a slightly enlarged kidney for a tuberculous organ, when it is in reality the one functional organ enlarged in a compensatory degree with the disease advanced on the other side.

Out of the 92 cases collected, the kidney was stated to be enlarged and palpable in 58, was not palpable in 26, and in 8 cases there is no mention of the fact. In four instances perinephric abscess was found present in addition to a tuberculous kidney, and in two cases a tumour in the loin was the first symptom noticed by the patient; in one of these a large tuberculous pyonephrosis was present, and in the other a tuberculous perinephric abscess.

Enlargement of the Ureter.—After a tuberculous renal focus has ulcerated into the renal pelvis, the lining membrane of the ureter becomes rapidly studded with tubercles. The mucous and submucous coats of the ureter become infiltrated and much thickened, as a result of which the ureter becomes shortened. Frequently, as well, there is some periureteritis, by which the ureter becomes fixed more firmly to the peritoneum covering it. I have been able in thin subjects to feel this thickened tuberculous ureter on deep palpation in the iliac fossa, and have been able to roll it under the fingers. It can be more readily felt, however, per vaginam or per rectum as a firm, hard cord in the lateral fornix of the vagina in the female, or to one side of the middle line and above the prostate and vesicles in the male; it is easily felt under an anæsthetic by bimanual

examination, and can be compared with the ureter of the other side. I have found the ureter thickened when there has been found to be no tuberculous infection in the bladder, and I look upon it as an important diagnostic symptom in renal tuberculosis. In 13 cases of unilateral renal tuberculosis under my care I found the ureter enlarged and palpable in nine cases, in four of which the bladder showed no sign of tuberculosis, although the ureteric orifice showed characteristic changes. Of the four cases in which the lower end of the ureter was not felt enlarged, in two the renal focus had been previously drained by nephrotomy, from which a tuberculous lumbar fistula had resulted.

Of the 79 cases I have collected from hospital reports, the ureter was found to be thickened in 21 instances. In 5 cases it is stated that the ureter was not palpable, whilst in 53 there is no mention of the examination.

Radiography.—In a few cases an indistinct shadow has been obtained by the X-rays of a tuberculous focus in the kidney. In one case under my care, Dr. Nolan, who kindly made a radiograph for me, reported that he obtained “an indistinct shadow which might be a calculus, but is more likely to be a tuberculous focus.” In 24 other cases a positive result was obtained in six instances.

General Symptoms.—There may be a slight elevation of temperature in the evening in renal tuberculosis in the more acute cases, but where caseation is the feature the temperature remains normal. Progressive loss of weight and anæmia are common. In cases in which ureteric obstruction occurs, there is increase of the lumbar pain and increase in size of the renal tumour, together with an apparent improvement in the urine, which, if the bladder and other kidney are unaffected, becomes normal until the ureteric obstruction is removed. If septic infection becomes added to renal tuberculosis, the disease runs a more rapid course, the temperature shows an evening rise, wasting is more marked, with loss of appetite, pallor and the general symptoms of suppuration.

Diagnosis of Renal Tuberculosis.—As in tuberculous disease elsewhere in the body, the early diagnosis of renal infection is of great importance, so that appropriate treatment can be carried out. The diagnosis is frequently, however, very difficult, as the symptoms in the early stage are very few and indefinite. When a patient has increased frequency of micturition, persistent pyuria in acid urine, together with slight hæmaturia, lumbar aching, loss of weight, and the presence of tubercle bacilli in the urine, the collection of symptoms are fairly distinctive, but, unfortunately, it is seldom that any case in an early stage gives rise to such a symptom-complex. In some cases increased frequency of micturition, with slight polyuria and albuminuria, may be met with, and renal tuberculosis may be suspected, but if the bacilli are not found in the urine, and there is no change found by the cystoscope of the ureteric orifice, the diagnosis becomes almost impossible. There may be slight loss of weight or an elevation of temperature above the normal in the evening without any local symptom to point to the kidney as the infected organ. If, however, the urine contains pus and blood, even in small amount, a thorough search should be made for the tubercle bacillus, and, if necessary, inoculation of the deposit of centrifugalised fresh urine made into guinea-pigs.

In many cases the symptoms, when the patient first presents himself, point, at first sight, to vesical disease. The increased frequency and painful micturition, with pus and blood in the urine in a young adult, strongly suggest infection of the bladder, and if the tubercle bacillus be found the case may be looked upon as one of vesical tuberculosis. However, primary tuberculosis of the bladder is much more rare than of the kidney, so that in all cases careful examination should be made of the kidneys and of the lower ends of the ureters per rectum or per vaginam for any enlargement or thickening, as these symptoms may all be present before there is any tuberculous infection of the bladder. The similarity between vesical and renal tuberculosis in an early stage is very marked, and many

errors in diagnosis between them have been made, but with a more complete knowledge of cystoscopy, primary renal disease is now more easily identified.

In the diagnosis of renal tuberculosis from *suppurative pyelonephritis* an accurate knowledge of the commencement and progress of the disease is of great assistance; the history of pre-existing urinary obstruction and sepsis in suppurative cases is usually obtainable, whilst the general condition of the patient, with rapid loss of weight, diminished excretion of urea, raised temperature and dry tongue, suggest a septic nephritis. Thickening of one ureter and the presence of tubercle bacilli in the urine should always be looked for in any doubtful case of pyuria, but it must be remembered that the bacilli are not readily found, so that many specimens may have to be examined or inoculation experiments on guinea-pigs carried out.

From Renal Calculus.—In the early stages in which a slight lumbar aching is the only symptom, it may be impossible to diagnose tuberculous kidney from calculous disease unless tubercle bacilli can be found in the urine. A radiogram which gives a sharp well-defined shadow would point to calculus, but it must be stated that a faint ill-defined shadow may be found with a caseous focus in the kidney. In cases in which pyelitis is present, either with stone or with tubercle, there may be some difficulty in diagnosis. Renal colic may be present in either disease, but the association of vesical irritability, of constant slight hæmaturia, which is unaffected by exercise or rest, is suggestive of tubercle. The hæmaturia of calculous disease is more likely to be influenced by exercise, or to occur after a more severe attack of renal pain, whilst vesical symptoms are infrequent. Ureteric thickening, as felt per rectum or per vaginam, is more likely to be due to tuberculosis, but must be carefully distinguished from an impacted stone in the lower end of the duct.

In the later stages of tuberculous disease in the male subject, it is not infrequent to find tuberculous nodules in the generative organs, so that examination should be made of the prostate,

vesicles and testes for any further evidence of tuberculous disease.

From Renal Growth, by the fact that in tuberculous disease the hæmaturia is rarely profuse, by the constant pyuria and by the presence of tubercle bacilli in the urine. Renal growths occur in young children, and in adults commonly over forty years of age, whereas renal tuberculosis usually occurs in young adults.

From Simple Movable Kidney, by the constant pyuria, which is not present in uncomplicated nephroptosis, and by the increased frequency of micturition.

In doubtful cases of tuberculous disease of the kidney, an *opsonic index* of the blood to tubercle bacilli may be estimated. If a marked variation from the normal be found, or if the index varies after a period of exercise, tuberculosis must be suspected somewhere in the body, but it gives no indication of a renal focus of disease unless other symptoms be present. The finding of a lowered index to tubercle in cases in which difficulty is found in the diagnosis of a case simulating renal tuberculosis, calculus or suppurative pyelonephrosis may be of assistance in the diagnosis.

When a diagnosis of renal tuberculosis has been made there may be doubt not only as to *which side is affected*, but also, if one side is known to be affected, as to the *freedom from disease and the functional capacity* of the *remaining organ*. A great deal can be learned from a cystoscopic examination in these cases, and it is no exaggeration to say that the diagnosis may rest entirely upon this examination. It has been shown by Hurry Fenwick that as soon as tuberculous disease affects the renal pelvis and ureter there is a characteristic change in the ureteric orifice of the affected side which in itself is sufficient evidence upon which to base a diagnosis of renal tuberculosis. This view has been upheld by Meyer, and my own experience in these cases is in strong support of this statement. As soon as pyelitis becomes established and pyuria exists, the ureteric orifice of the affected side becomes changed from

the normal slit-like opening in the bladder: the margins of the orifice become thickened and œdematous, and the orifice becomes rounded, puckered, and, later, patulous. With the thickening and infiltration of the ureter, the duct becomes shortened, so that the orifice becomes drawn out, appearing at first of a horse-shoe shape. With the gradual progress of the disease the orifice becomes more dragged upon and retracted, so as to appear at the upper part of a gutter or tunnel, or at the summit of a conical-shaped recess, and at the same time to be altered from its normal position in relation to the trigonal area of the bladder, being drawn upwards and outwards. Meanwhile, the vesical mucous membrane around the orifice becomes congested, thickened and œdematous, whilst commonly the area above and outside the orifice, that is, the part in relation to the terminal or intramural portion of the ureter becomes reddened and thickened. These congested areas of vesical mucous membrane show at first no evidence of the deposition of submucous tubercles, but later they may be present as small greyish elevations either limited to the area around the orifice or elsewhere in the bladder. Finally, several of these tubercles may coalesce and break down to form a typical tuberculous ulcer. Thus it will be seen that in comparatively early stages of renal tuberculosis there is a change in the appearance of the ureteric orifice of the affected side before there is any sign of vesical disease. This change is not present in other forms of renal disease, and its presence not only shows which kidney is affected, but is very strong presumptive evidence of the disease being tuberculous.

In the cases I have collected, cystoscopic examination is mentioned in 40 cases. In these, small deposits of vesical tubercle were found in 12 cases, and the appearance of the ureteric orifice of the affected side was noted in 37 cases: of these, 3 were said to be normal, 5 were dilated, 13 were œdematous, congested or patulous, and 16 were said to be retracted, drawn up or displaced.

Before leaving the question of diagnosis, another important question arises upon which the treatment of the case in part depends, namely, the *condition of the other kidney*. It is necessary to have an accurate knowledge of the functional capacity of the remaining organ, which may be free from tuberculous infection, but which may be the seat of nephritis or lardaceous disease. The cystoscopic appearance of the ureteric orifice may show the latter to be normal, and that the urinary efflux from it is clear, and in normal forcible jets, but it gives no indication of the quality of the urine excreted. For this purpose the urine must be obtained separately from each kidney, and a careful analysis made. I have written elsewhere (*Practitioner*, March, 1910) upon the estimation of the functional activity of one kidney, and may here briefly indicate the mode of procedure. The urine may be collected separately from each kidney either by the urinary separator or by ureteric catheterisation, and of the two the latter method is preferable. This is especially true if there is any tuberculous infection of the bladder, when the separator may cause bleeding from contact with the infected vesical area, and so give an erroneous result. If it is only necessary to determine the functional capacity of the unaffected kidney, that ureter only need be catheterised, and the urine from the diseased side collected from the bladder. It is useless to pass a catheter into the ureter of the side affected, as it may become blocked by purulent debris. It has been urged that when the bladder is infected, the passage of a catheter into the healthy ureter may be an unjustifiable risk, but this is certainly more apparent than real, as the catheter can be passed straight into the ureter without touching any infected vesical mucous membrane. If the bladder is seriously involved, the necessity to catheterise a ureter will seldom arise.

The examination of the separated urines will consist of an estimation of the contained solids, a microscopical examination of the centrifuged deposit for pus and tubercle bacilli, and the estimation of the freezing point compared with that of the

blood. The separation should be carried on for some hours, if possible, so as to eliminate any physiological error due to temporary changes in excretion from the mere presence of a catheter in the ureter, and to the varying physiological rates of urinary secretion. A further test may be carried out by estimating the rate of elimination by the kidney of such substances as methylene blue, indigo-carmin, or phloridzin. If methylene blue is used, an intramuscular injection into the buttock of 15 minims of a 5 per cent. solution is made, and the depth of colour of the dye in the urine and the amount of colourless chromogen excreted at short intervals noted. It is found that in a normal functional kidney the urine becomes tinted with a green coloration within thirty minutes of the injection, and rapidly becomes of an emerald green colour in the succeeding two hours, whilst the chromogen shows a more rapid elimination, being converted by boiling with acetic acid into a green in twenty minutes, and to a deep emerald or blue in forty-five to sixty minutes.

If there is albumen or pus in the urine from the ureteric catheter, if the amount of urea and the rate of elimination of methylene blue be diminished from the normal, or if the freezing point of the urine is raised, whilst the freezing point of the blood is lowered beyond -59° , the functional capacity of the organ under review must be deemed lowered, and the removal of the diseased organ would be accompanied by a severe risk of death from uræmia.

Treatment.—Tuberculosis of the kidney must be treated in the same manner as tuberculosis in any other part of the body, partly by general hygienic principles and partly by surgical measures. Doubtless in some of the earliest cases cure may be obtained by medical therapeutics, but unfortunately the disease can be rarely recognised in this early stage or until the renal focus has involved the calices or pelvis. Post-mortem records of cases, too, show a very small number in which healed tuberculous foci are found in the kidney, but with the more recent form of treatment by vaccines, it is possible that

a larger number of cases may be cured in the future by this means. In all cases of early disease of one kidney, a course of treatment by vaccine, with due regard to the opsonic index, together with residence in a bracing climate, and the exhibition of urinary disinfectants such as urotropin, sandalwood oil, or creosote should be given a trial.

In cases which come under observation at a later stage, when the ureter or even the bladder has become infected, or in which, in spite of medical treatment, the symptoms increase, surgical measures must be employed. The exact operation to be performed depends in a great measure upon the extent of the disease, but the attempt should be made to remove all the diseased tract whenever it is practicable. Thus, the diseased kidney may be removed, the ureter resected to within an inch of the bladder, whilst in some few cases the whole ureter with the immediately adjoining portion of the bladder has been removed with success. This, however, is rarely necessary, for with the recent methods of combating tuberculosis, it has been found that when the bladder has become infected secondarily to the kidney, the removal of the diseased kidney and ureter, with subsequent treatment for the vesical infection, gives excellent results. Thus, in one case under my care, whom I saw with Dr. Hale White, where the bladder was somewhat extensively infected from a primary tuberculosis of the left kidney, the removal of the kidney and ureter in March, 1906, with subsequent treatment by vaccine, has been followed by a most gratifying result; the patient has put on weight, has no pain or increased frequency of micturition, and the urine is normal. The bladder on cystoscopic examination shows some scars of healed tuberculous ulceration. In several other cases equally good results have been obtained, but the interval after the operation has been shorter than in this case. Thus, if the disease be localised to one kidney and ureter, the removal of the infected area gives a good prospect of permanent cure.

Before any operation on the diseased kidney is undertaken, it is necessary to obtain the knowledge of the condition and

the functional capacity of the other organ, and I have already described the methods by which this may be estimated.

1. *Nephrectomy* is the ideal operation for tuberculous kidney, provided that the remaining organ is normally active. Nephrectomy, however, must be supplemented by resection of the ureter, which will be found in most cases already infected. To ligature the infected ureter below the kidney is to invite the formation of a tuberculous fistula, so that in all cases it is necessary to remove as great a length of the ureter as possible. It has been recommended to carry out this operation in two stages, first, to remove the kidney and some time later to remove the ureter; this is quite unnecessary, however, for the removal of the ureter occupies little time and does not increase the risk of the operation to any extent. In my earlier operations, I exposed the kidney from the usual oblique lumbar incision and separated it from the perirenal tissues until the hilum was reached. The renal vessels were then separated from the ureter and renal pelvis, ligatured with plaited silk and divided, care being taken not to open the renal pelvis. The parietal incision was then prolonged downwards and forwards in front of the anterior iliac spine to the mid-Poupart plane, and the peritoneum stripped from the iliac fossa. The ureter was traced down into the true pelvis, ligatured as low as possible, divided, and the stump scraped and painted with phenol. In the male the ureter was removed in this way to within an inch of the vesical opening, and in the female it was divided in the base of the broad ligament at the situation of the uterine vessels. I found, however, from the free division thus made of the parietal muscles, that the patient was left in some cases with a weakened abdominal wall, so that I have modified the operation in such a manner as to leave a broad bridge of muscle undivided. I first expose the kidney by the oblique lumbar incision, separating the peritoneum at the anterior part of the incision forwards. The renal vessels are then ligatured and divided, and the upper part of the ureter separated downwards. After arresting any bleeding and providing for drainage, the

kidney is tucked down into the lower part of the wound, and the incision sewn up in layers. The patient is then turned into the dorsal position, and an incision made in the iliac fossa parallel to Poupart's ligament, as for the removal of the appendix, dividing the muscles in the line of the incision. The peritoneum is not opened, but is separated inwards from the iliac fossa, when the ureter is quickly identified as it crosses the iliac vessels and adherent to the peritoneum; a little separation upwards soon joins the line of separation from above, and the kidney, lying loose in the retroperitoneal tissues, is delivered from the iliac incision. The lower part of the ureter is then separated and ligatured as before as low as possible in the pelvis and removed. In this manner, two comparatively short incisions are made through the muscular wall of the abdomen, separated by a bridge of undivided tissues, and the ultimate result as regards the strength of the abdominal wall is much more satisfactory. I have now removed the kidney and ureter by these methods in ten cases, in each of which the terminal stump of the ureter has been scraped and painted with phenol. The lowest angle of the inguinal incision was drained in each case for from 24 to 36 hours with a small tube leading down to the divided ureter, and in only one case did I have any trouble from tuberculous infection in the wound which required subsequent excision. One case died from complete suppression of urine thirteen days after operation, when it was found that the remaining kidney was the seat of interstitial nephritis. The subsequent histories of the other cases will be found in the report of each case. Keyes states that in a collection of 98 cases of tuberculous kidney, 64 were cured after nephrectomy. 30 of whom had remained well for upwards of three years.

2. *Partial Nephrectomy* has been recommended by some authorities to remove a localised area of renal infection. It will be found, however, that tuberculous infection in the kidney is rarely localised to one pole, but that the remaining parts of the organ show deposits in earlier stages. These, however, might clear up under suitable hygienic conditions after the pri-

mary focus has been removed, but in my opinion, if the ureter shows any thickening or other sign of infection, it is better to remove both the kidney and the ureter than to rely upon a partial resection of the kidney. Morris, Israel and Czerny have performed this partial operation in nine cases, but in four of them it was found necessary to remove the remaining part of the kidney subsequently.

3. *Nephrotomy* must be regarded as a palliative measure to be undertaken to relieve the symptoms when a primary nephrectomy is contraindicated. Thus, in cases in which both kidneys are diseased and in which a tuberculous pyonephrosis is giving rise to pain or fever from the retention of pus in the kidney, nephrotomy may be performed; again, when the patient's condition will not bear the extra risk of nephrectomy, or when there is reason to doubt the functional capacity of the remaining organ, nephrotomy may be undertaken as a preliminary measure to a subsequent nephrectomy. This secondary nephrectomy should not be delayed longer than is necessary to relieve the septicæmic condition, or than to prove the remaining kidney is functionally active, owing to the dense adhesions which may be formed to the surrounding tissues. Nephrotomy has, on the other hand, by free drainage, proved curative in some cases, and Keyes states that seven out of fifty cases of nephrotomy for tuberculous disease were cured by this means. In one case under my care a small focus of disease in the lower pole of the kidney was well scraped and drained, and under subsequent vaccine treatment the disease appears to be arrested. Two other cases came under my care in whom a previous nephrotomy had been performed. In one case (R. F.) the urine from the renal fistula caused so much trouble from leakage that I removed the kidney, which was found to be densely scarred, but showed no area of recent disease, the cutaneous fistula opening directly into the renal pelvis. In the other case, the kidney was riddled with tuberculous foci, but was so adherent to the surrounding tissues that I could only remove it by subscapular nephrectomy.

Is Vesical Infection a contra-indication to Nephrectomy? This depends upon the extent of the vesical infection. If the vesical disease is limited to the area around the ureteric orifice, or is but an early deposition in the bladder, I would not hesitate to advise nephrectomy and ureterectomy, provided the remaining kidney is proved active and normal. In these cases the diseased kidney is a source of danger to the patient, and is probably too extensively diseased for any hope of recovery by vaccine or other form of medical treatment. Further than this, the constant passage of pus and tuberculous material into the bladder merely aggravates the existing early infection, besides which the general condition of the patient suffers from toxic absorption. In these cases the removal of the kidney as the primary source of infection will not only improve the patient's general condition, but will put him into a much better condition to overcome the vesical infection, whilst the treatment of the latter by vaccine will, in many cases, effect a cure. The majority of my own cases have not been operated upon sufficiently long ago to deduce results, nor am I able to quote any figures as to the prospect of cure in these cases, as the records of cases do not give sufficient detail as to the cystoscopic evidence of vesical disease, but the improvement, both in the symptoms and in the cystoscopic appearance of the bladder in my cases after operation, is so apparent that I do not hesitate to advise the operation.

The importance of a preliminary estimation of the functional activity of the other kidney before any operative measure is undertaken cannot be too strongly insisted upon. Renal tuberculosis may be so insidious in its onset that few symptoms may be evident until the disease is fairly advanced or until both kidneys are infected. One of my earlier cases died of uræmia after nephrectomy from interstitial nephritis of the remaining kidney, which would probably have been detected had the methods at present in use been applied. Watson states that in one series of 362 cases of nephrectomy in which the functional capacity of the other organ was not estimated, the

operative mortality was 35 per cent., whereas in a second series of 292 cases in which the examination showed that the kidney was active, the operative mortality fell to 7·8 per cent.

SUMMARY OF TREATMENT.

1. *Medicinal* in early cases, including hygienic and dietetic conditions, vaccine treatment and the exhibition of urinary disinfectants, such as sandalwood oil, creosote, urotropin, etc.

2. *Surgical*.—*Nephrectomy and Ureterectomy* as a radical measure, provided that

- (a) the tuberculous infection does not involve the other kidney.
- (b) the other kidney is proved functionally active, and estimated to be able to take on the function of both organs.
- (c) there are no tuberculous lesions of such extent elsewhere in the body as to render nephrectomy useless.

Nephrotomy, to relieve any urgent symptom due to pyonephrosis, to be followed by nephrectomy, if suitable; or, purely as a palliative measure, when nephrectomy is contra-indicated. Rarely in very early cases of tuberculous disease in which a small focus may be scraped and drained.

In conclusion, I wish to thank not only my colleague Mr. Ernest Miles, who has allowed me to record a case under his care, but also the members of the staff, both of Guy's and St. Peter's Hospitals, for their kindness in allowing me to have access to the reports of cases of renal tuberculosis that have been in these hospitals during the last ten years. I wish also to tender my thanks to Dr. English, to whom I am indebted for the photographic records of the specimens removed at operation.

REPORT OF CASES.

CASE 1.—Tuberculous kidney and ureter. Early vesical infection. Operation refused.—Miss M. was seen in June, 1907, in consultation with Mr. L. A. Dunn. She had had attacks of right-sided renal colic, followed by hæmaturia, enough to cause distinct coloration of the urine; during the attack she had constant desire to pass urine. In the intervals between the attacks of colic there was dull aching pain in the right lumbar region, but no pain on the left side. Frequency of micturition was increased to two-hourly by day and three times during the night. The patient had not lost weight, had no cough nor sweating, and her temperature was normal. *On examination.*—There was increased tenderness in the right renal area on deep palpation, but the kidney was not felt. No tenderness on pressure over left kidney. The urine was pale and opalescent, acid in reaction, sp. gr. 1018. Pus corpuscles and a few red blood discs were found on microscopic examination. Under ether, a cystoscopic examination was made. Distension 10 ounces easily. There was generalised cystitis; no ulceration was seen, but to the outer aspect of the right ureteric orifice were two pale rounded nodules which looked most suspiciously like submucous tubercles. The right ureteric orifice was rounded and rigid, situated upon a raised area of thickened mucous membrane. The left ureteric orifice was normal, but no urinary efflux was seen from either ureter. Per vaginam, the right ureter was easily felt to be thickened; the left ureter was normal. From the examination the case was diagnosed as one of tuberculous nephritis rather than one of renal calculus, which had been suspected. Four days later, Dr. Eyre found the opsonic index of the blood to tubercle to be 1.15, but he was unable to find tubercle bacilli in the urine. The curve of opsonic index after an injection of tuberculin was, however, similar to that usually obtained in tuberculous cases. Further examination of the urine was made by Dr. Eyre, when undoubted tubercle bacilli were found; treatment with vaccine was then commenced. On October 5th, 1907, I again saw Miss M. in consultation with Dr. Pitt and Mr. Dunn. During the interval she had gained 5 lbs. in weight, but had had recurrent attacks of renal colic on the right side, followed by bright hæmaturia. The last attack occurred on October 3rd, and the urine remained blood-stained for six hours. The frequency of micturition had further increased to four or five times during the night, and there was slight urethral pain following micturition. *Cystoscopy* under cocaine. Distension 8 ounces. There was general subacute cystitis, more marked over the right side of the bladder. The right ureteric orifice was rounded, with raised patulous lips. There was no ulceration, but submucous tubercles were present on the right lateral vesical wall. The left orifice was normal, and clear urine was seen emitted with forcible efflux. *Segregation of Urines.* Luys' instrument. From the left side there was a copious flow of clear urine, about 8—10 drops at a time at intervals of about 30 seconds. After rejecting the first, a full test-tube of clear urine was



Primary Unilateral Renal Tuberculosis.



CASE 2.—A. T.—Large tuberculous focus in median portion containing thin pus. Caseous area in lower pole, and smaller foci in upper pole. Renal pelvis infiltrated with tubercle.

collected. From the *right* side, urine was turbid and opalescent. Flow was continuous, drop by drop, without any definite rhythm. During the same time in which a full test-tube was collected from the left side, only half the amount was collected from the right. Unfortunately no examination of the urine from each side was made for urea estimation or for bacilli. The patient would not allow any operation to be performed.

CASE 2.—Tuberculous kidney and ureter. Vesical infection. Nephrectomy and ureterectomy.—A. T., female, æt. 35, was admitted under my colleague, Mr. Miles, for hæmaturia in March, 1908. *Family history*.—Parents alive and well. One sister died at age of 22 from phthisis. *Personal history*.—Patient is married and has four children. She was well until two years ago, when she first noticed pain in the right side of abdomen and right iliac fossa, aching in character, and accompanied by increased frequency of micturition. There was no colic, but the urine was often tinged with blood. These symptoms passed off, but her urine was frequently tested by a doctor, who said she had "weakness of the kidneys." Three months ago she had a somewhat profuse attack of hæmaturia, since when the urine has been almost constantly tinged with blood. During this time there has been gradually increasing frequency of micturition up to half-hourly during both day and night. There was pain in the right iliac fossa. Three weeks ago she had a severe attack of pain in the right subcostal area, lasting forty-eight hours, with vomiting, sweating and faintness, and since then has had constant aching in the right loin. The urine is tinged with blood, intimately mixed throughout micturition. She has never passed a stone, nor has there been any pain in the left side. She has had no cough or night sweats, but has lost weight during the last year. *On examination*.—Patient is a well-nourished woman. Temperature and pulse normal. There is marked tenderness on palpation in the right loin, where the kidney can be felt as a slightly enlarged, rounded, movable organ, descending freely on inspiration, when it can be easily grasped bimanually. The surface is smooth, with rounded outline, and a tense, elastic feel, but no fluctuation in it can be observed. From the lower and inner margin an indistinct, rounded cord could be felt to extend down to and over the pelvic brim in the situation of the ureter. The left kidney could not be felt. Per vaginam, the lower end of the right ureter was distinctly thickened. The left ureter felt normal. Urine, slightly tinged with blood; acid; sp. gr. 1022. Pus present. Tubercle bacilli were present in the urine. No abnormal physical signs were present in the thorax.

March 19th, 1910. *Cystoscopy*—cocaine. Distension only 4 ounces, without pain. Generalised subacute cystitis, with scattered hæmorrhagic tubercles around the right ureteric orifice. Small, well-defined tuberculous ulcer at fundus. The right ureteric orifice was rounded, patent and retracted; no efflux of urine was seen from it. The left orifice was small, and clear urine was seen emitted in vigorous efflux. *Segregation*. Lays' instrument. Urine drawn off from bladder contained 2·8 per cent.

urea. No urine was collected from the right side during twenty-five minutes the instrument was retained. From the left side clear urine was obtained in rhythmic jets containing 3.2 per cent. urea. As the left kidney was acting well, it was decided to remove the right kidney and ureter as the primary source of infection, and to treat the vesical infection subsequently with tuberculin.

March 26th, 1908. *Operation.* The right kidney was rapidly exposed by an oblique lumbar incision and brought up into the wound. It was enlarged, with areas of soft, fluctuating prominences where the renal tissue was very thin. The ureter was much thickened, the upper end being nearly as large as a forefinger. The renal vessels were ligatured and divided, and the incision prolonged downwards and forwards in front of the iliac spine. The parietal peritoneum was stripped up from the iliac fossa, and the thickened ureter traced down to the level of the broad ligament, where it was ligatured and divided and the terminal stump painted with phenol. The wound was sewn up with a small drainage-tube at each end, the lower tube leading to the ureteric stump. The organ removed showed no perinephritis. There was a large thin-walled cyst in the median portion of the kidney containing thin pus, and lined by floccular granulations. At the lower pole was an older cavity filled with caseous material, and smaller foci in the upper pole. The renal pelvis was much thickened by tuberculous infiltration. The wound healed without trouble, and the patient left the hospital much improved. She did not appear again until October, 1908, when the frequency of micturition had increased to hourly by day and by night. She had noticed also occasional hæmaturia. Tuberculin treatment was commenced, and in June, 1909, she was improved. There had been no hæmaturia since April, but the frequency remained excessive, and she had pain after micturition. July 29th, 1909. Patient can hold urine for about an hour and a half. No hæmaturia, but urine still contains pus. Tubercle bacilli are still present in urine. Has not lost weight.

CASE 3.—Primary renal tuberculosis. Early vesical infection. Nephrectomy and ureterectomy.—C. E., female, æt. 31, was admitted under my care in September, 1908, for increased frequency of micturition. The patient first noticed increased desire to micturate in September, 1907. There was no pain at this time, but she noticed that her urine was turbid and contained stringy pieces. The increased frequency of micturition varied from time to time, but she continued her work as a domestic servant until May, 1908. In July she first noticed an aching pain in the left loin, which has been constantly present since then. There has been no colic, and the urine has never been blood-stained. The frequency of micturition has been more marked during the last two months, and amounted to hourly by day and four or five times at night. She had lost weight during the last six months. *On examination,* the patient was a thin anæmic person. On palpation in the left loin, the left kidney can just be felt to descend on inspiration. The lower pole seems to be enlarged and rounded, and pressure causes pain. The right kidney could also be felt to descend on inspiration.

Primary Unilateral Renal Tuberculosis.



CASE 3.—C. E.—Large tuberculous cavity in upper pole of kidney, communicating with the renal pelvis, which is thickened and tuberculous. Small foci of tubercle in renal parenchyma.

Per vaginam, neither ureter could be felt to be thickened. Urine, turbid; acid, sp. gr. 1016. Pus and albumen present in small amount. Urea 1·8 per cent. Tubercle bacilli were found present. *Cystoscopy* under ether. Distension 8 ounces easily. The vesical mucous membrane was congested in the left lateral wall and in left basal area. On the outer aspect of the left ureteric orifice were a few submucous tubercles grouped together, and to the left of the fundus was a small, shallow, tuberculous ulcer. The left ureteric orifice was enlarged, of horse-shoe shape, with rigid thickened margins, and from it urine containing shreds of muco-pus was slowly expressed. The right ureteric orifice was normal, and from it clear urine was emitted in good efflux. In four consecutive days the total urea elimination amounted to 380, 415, 400 and 392 grains. *Colour test.* September 23rd. The right ureter was catheterised, and an hour later 15 minims of a 5 per cent. solution of methylene blue was injected into the gluteal muscles. The urine collected from the ureteric catheter showed a distinct coloration in 35 minutes, and became of an emerald green colour in one hour. The urine from the left side withdrawn from the bladder showed no coloration after an hour and three-quarters, although a small amount of colourless chromogen was present. It was decided that the primary focus of disease was in the left kidney and that the right kidney was not infected, and was functionally active.

Operation, September 28th, 1908. The left kidney was rapidly exposed from an oblique lumbar incision, and brought up into the wound. It was slightly enlarged, and at the upper pole was a large, soft, fluctuating area. The upper end of the ureter was thickened and rigid. The renal vessels were ligatured and divided, and the incision prolonged downwards. The parietal peritoneum was reflected and the ureter separated into the true pelvis, some difficulty being encountered in the base of the broad ligament from bleeding from a uterine vein. The ureter was divided as low as possible between two catgut ligatures, and the terminal end scraped and painted with phenol. The wound was closed with a double layer of sutures, a drainage-tube being left at each end. The operation was completed in 35 minutes and was well borne. The progress of the patient was uneventful; the tubes were removed after 36 hours, and the wound healed rapidly. On November 5th, 1908, the patient was free from pain, and the frequency of micturition had decreased to three hourly during the day and twice at night. On cystoscopy there was an area to the left of the fundus the size of a three-penny piece covered by mammillated mucous membrane: radiating from it were raised bands of mucous membrane formed by the contraction of a healing ulcer. There was some congestion around the left ureteric orifice; the rest of the bladder wall was normal. Treatment by vaccine was commenced soon after the operation, and was to be continued for several months. In January, 1909, she had a small tuberculous abscess at the lower end of the scar which was opened and scraped. The frequency of micturition remained the same, but her vesical pain was much diminished by sandal wood oil. In July, 1909, the frequency of micturition averaged every 3—4 hours during the day and once at night, but she had slept through several nights without

passing urine. She had gained 7 lbs. in weight in six months. The urine was acid; sp. gr. 1016; was clear, but contained a trace of albumen. She had improved in every way since the removal of the kidney. January, 1910: Frequency of micturition is now normal, and she is not troubled at night. Urine clear and free from albumen. Is still having injections of tuberculin, 1/2000 mg. once a week.

September, 1910: Patient continues to do well. Frequency of micturition is normal, and she can retain urine for eight hours. Urine is free from pus and albumen. Has increased nearly a stone in weight in twelve months.

CASE 4.—Tuberculous left kidney and ureter. Early vesical infection. Nephrectomy and ureterectomy.—Father D. M., æt. 31. Seen on March 20th, 1906, in consultation with Dr. Hale White, for increased frequency of micturition. Two years previously he was rejected for life insurance owing to albuminuria; no other symptom at this time. In September, 1905, he first noticed increased frequency of micturition, together with smarting in the glans penis, and the appearance of a few drops of blood at the end of micturition. These symptoms then abated until two months ago, when they reappeared and have become more severe. The frequency of micturition amounted to hourly by day and two hourly by night; he had constant aching pain in the left lumbar region, but had had no attacks simulating renal colic; was slowly losing weight, and distressed by his restless nights. No cough or night sweats. On examination, patient was a thin subject, pallid complexion. *Abdomen*—slight tenderness over both renal areas on deep pressure. The left kidney was not felt, but the lower pole of the right kidney could be felt on deep inspiration. Liver not felt. No tumour. No abnormal physical signs in thorax. Testes normal. Per rectum—small, hard, rounded nodule felt in left prostatic lobe. Nil in vesicles. Left ureter felt very distinctly thickened in lower $1\frac{1}{2}$ inch. Urine acid, sp. gr. 1018; albumen, pus and blood present in small amount. Tubercle bacilli present. *Examination under anæsthetic*. Cystoscopy. Distension of bladder to six ounces. Early infection of bladder on left lateral wall, where a small group of tubercles were seen, some of which had recently broken down. Some congestion of trigonal area. Rest of bladder wall free. Left ureteric orifice rigid, patent, "golf hole" orifice, with some œdema around. Flakes of muco-pus seen emitted with faint efflux. Right orifice rather large, but lips not œdematous. Normal efflux of clear urine in good jet. March 25th. Opsonic index to tubercle, 59 (Dr. Eyre). Luy's segregator not used in this case owing to the existing vesical infection. During the week patient was under observation the daily quantity of urine passed varied from 38 to 57 ounces. Specific gravity remained fairly constant between 1018 and 1022, and urea (total daily secretion) averaged 430–450 grains. At a further consultation it was decided to remove the left kidney and ureter, so as to remove the primary focus of disease and to treat the remaining early vesical infection subsequently by vaccine treatment. Tuberculin, T. R., 1/2000 mg., was given, and the opsonic index raised to 1.1, and on April 3rd, 1906, he was operated upon.

An oblique lumbar incision was made and the muscles divided. The kidney was quickly exposed and brought up into the wound. It was not enlarged, but on the anterior aspect was a rounded, prominent, soft area about an inch and a half in diameter. The ureter was next defined, and found to be thickened, appearing as a firm, infiltrated cord the size of a lead pencil. The ureter was separated from the vessels of the pedicle, and the latter ligatured with plaited silk and divided. The wound was now prolonged downwards and forwards in front of the anterior iliac spine, and the parietal peritoneum stripped up from the iliac fossa. The ureter was separated over the iliac vessels and ligatured with catgut about two inches below the level of the pelvic brim; it was clamped and divided, the distal stump being painted with pure phenol. All bleeding was arrested and the wound sewn up in layers, a small drainage-tube being placed in the lower angle and another into the renal bed. Recovery from the operation was rapid, the total amount of urine passed in successive days after the operation being 16, 26, 30, 28, 33, 28, and 36 ounces. The lumbar pain entirely disappeared and the increased frequency of micturition lessened to three hourly by day and twice at night. On May 1st he was well enough to get up from bed, had no pain of any sort, and could hold urine for four hours without discomfort. Injections of tuberculin, T. R., 1/2000 mg. were commenced, and the opsonic index maintained at 1·2. He left for the seaside on May 20th. In October, 1906, the patient was much stronger and had put on over one stone in weight. The vesical irritability was but slight, and he had on occasions held his urine for six to seven hours. The urine contained a trace of albumen; sp. gr. 1022; and under the microscope a few pus cells and red blood discs were found. No tubercle bacilli could be found in the centrifugalised deposit. The wound was soundly healed, and on rectal examination the small nodule in the left prostatic lobe was no larger than in March. All treatment was discontinued and patient led an open-air life in the South of Ireland. In March, 1907, he again came over, as he had seen a trace of blood in his urine at the termination of micturition. Frequency of micturition amounted to four hours by day and twice at night, but he had no pain of any sort. Urine was faintly turbid; acid; sp. gr. 1020; and tubercle bacilli were found after centrifugalising. The opsonic index to tubercle was ·84. On a further cystoscopic examination a small tuberculous ulcer was seen on the left lateral wall, above and outside the flattened ureteric orifice; the ulcer had a yellowish base and was surrounded by radiating bands of cicatricial mucous membrane, suggesting a recent implantation of tubercle on the scar of a healed ulcer. The right ureteric orifice was normal, and clear urine was seen emitted in vigorous efflux. Injections of tuberculin vaccine were carried out by Dr. Eyre, and the index maintained above normal. In July, 1907, he wrote, "Since I last saw you I have been in good form again. I have passed a sign of blood only once or twice, and once a little dry crust as off a sore, but otherwise the water has been clear. The frequency varies somewhat; sometimes I am almost normal in that respect." When seen again in May, 1908, he had put on weight, and could hold urine for four to five hours. The prostatic nodule remained the same, and the patient

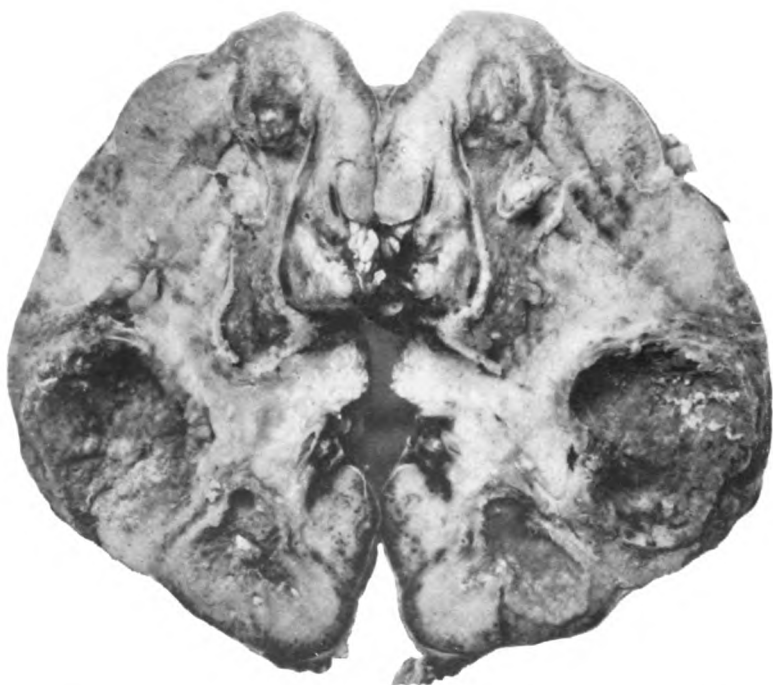
was in excellent health. The ilio-lumbar wound was somewhat weak, bulging on coughing, but did not interfere with the patient playing golf. The urine contained a trace of albumen and pus, but no blood, and no tubercle bacilli could be found. In June, 1909, he was again seen, and complained of tenderness about the left external abdominal ring. His index to tubercle was lowered to '68, and he did not respond to the injections. Frequency of micturition was not increased above four times in the day and once at night, and the urine only contained a trace of pus. Over the left side of pubis was a fluctuating swelling which was opened and found to be a tuberculous abscess, probably arising from the vas deferens. It quickly healed after scraping. There was no other sign of tubercle elsewhere in the body.

March, 1910. Patient seems quite well. Frequency of micturition is normal, and there is no pain or discomfort of any sort. Urine is clear, but contains a trace of albumen. Has increased 7 lbs. in weight.

CASE 5.—Tuberculous kidney and ureter. No vesical infection. Nephrectomy and ureterectomy.—C. S., female, *at.* 22, was seen with my colleague, Mr. Ernest Miles, on February 11th, 1907. Three years ago she first noticed pain in the epigastrium, which she attributed to a strain. This pain went off, and eighteen months ago she first noticed pain in the back, chiefly in right renal area. This pain was at first of an aching character, but soon after the onset she had an acute attack of renal colic in the right side, accompanied by sweating, vomiting and faintness. This pain commenced suddenly, lasted from one to one and a half hours, and terminated as suddenly as it commenced. These attacks recurred at varying intervals. Micturition was at first normal, but with the onset of pain the urine was noticed to be turbid and to deposit a white sediment. There was no hæmaturia at any time, nor was the urine foul. During the last six months frequency of micturition has been increased, and when seen amounted to two hourly by day and three times at night. There was no pain on micturition. The patient had lost weight during the last six months. *On examination.* Thin, fair-haired girl. Anæmic. There was slight tenderness on pressure in the right renal angle. The right kidney was movable and easily pushed down from the renal fossa. It was slightly enlarged, smooth and tender on pressure. The left kidney could be just felt on deep inspiration. No abnormal physical signs were present in the lungs. *Per vaginam*, the right ureter was felt to be slightly thickened, and could be rolled between the fingers on bimanual examination. Urine acid, *sp. gr.* 1018: deposit of pus.

February 14th. *Cystoscopy.* Distension 10 ounces. There was some congestion about the right ureteric orifice, extending to the trigonal area. The rest of the bladder wall was pale. No ulceration or sub-mucous tubercles seen. The right orifice was patulous, with raised oedematous margins. No urine was seen to come down from it. Left orifice was normal, and urine flowed from it in clear forcible efflux. A specimen of urine drawn off to-day was found to contain tubercle bacilli.

Primary Unilateral Renal Tuberculosis.



CASE 5.—C. S.—Thick-walled tuberculous cavities. Mucous membrane of renal pelvis studded with tubercles.

February 20th. *Segregation* of urine. Luy's instrument. From left side clear urine in rhythmic jets, 32 c.c. collected; acid; sp. gr. 1018; urea 1.8 per cent. No albumen nor pus present. From right side, urine turbid and opalescent; flowed in irregular drops; amount 24 c.c.; faintly acid; urea .8 per cent.; contained pus; a few red blood corpuscles and tubercle bacilli were present. February 24th. *Colour cystoscopy*. An injection of indigo-carmin was made into gluteal muscles. The urine from the left side was found to be distinctly coloured in 25 minutes, but there was no coloration of the right urine after two hours.

February 28th, 1907. *Operation*. The kidney was exposed by an oblique lumbar incision, which was afterwards prolonged downwards and forwards into iliac region. The kidney was enlarged by several soft fluctuating areas, which were found to contain thin purulent urine. The renal vessels were ligatured and divided, and the parietal peritoneum stripped up from the iliac fossa. The ureter was isolated into the pelvis, ligatured under the broad ligament and divided, the stump being painted with phenol. The wound was closed in layers, with a small drainage-tube at either extremity. Convalescence was uninterrupted, and when the patient left six weeks later, the scar was soundly healed. The urine was clear, and only contained a trace of albumen and pus, and the frequency of micturition had decreased to four times by day and once at night. The kidney was found on section to contain several tuberculous abscesses lined by thick granulation tissue. The pelvis was thickened and studded with submucous tubercles. August 23rd, 1909. Patient examined to-day. She has no pain of any sort and feels quite well; she can work all day without inconvenience, and has increased in weight. Frequency of micturition is normal, and she is not troubled to get up at night. The ilio-lumbar scar is firmly healed. The urine is acid; sp. gr. 1016; and contains neither pus nor albumen.

March, 1910. Patient reported herself to be quite well. She has no pain of any sort, urine is clear, and she says she can do anything.

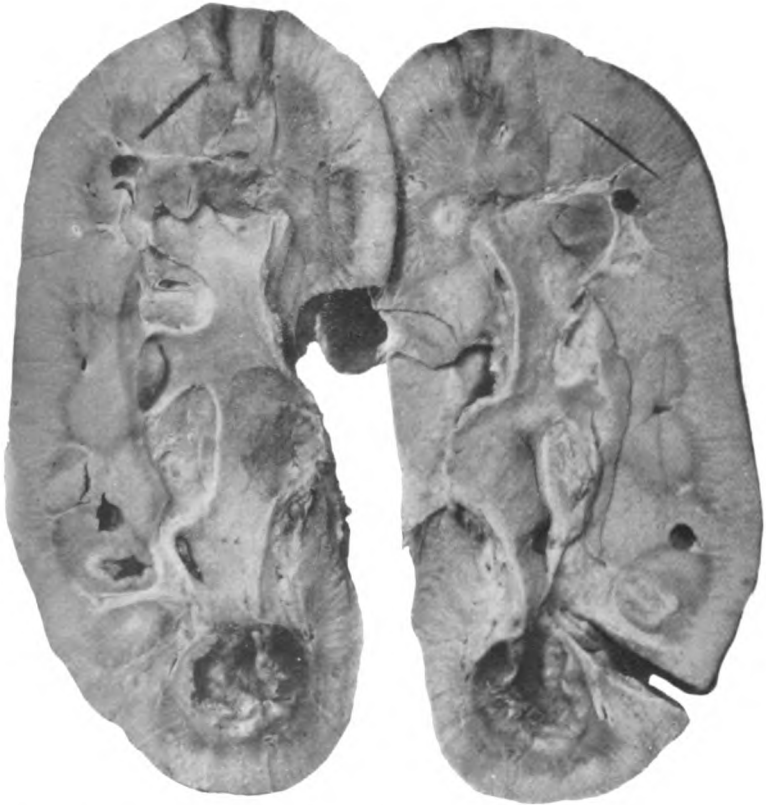
CASE 6.—Tuberculous nephritis and ureteritis. Operation followed by suppression of urine and death.—Mrs. J., æt. 35, was seen in February, 1905, with Mr. Targett. Patient had been well until October, 1904, when she "caught a chill" about a month after her second confinement. She first noticed some blood-stained shreds in the urine, quickly followed by increased frequency of micturition, with slight urethral pain after emptying the bladder. The appearance of blood in the urine recurred occasionally, and in December, 1904, she noticed an aching dull pain in the right lumbar area. This had recently become more severe, but there were no attacks of colic. She had lost weight during the last six months. The uterus and appendages were normal, but Mr. Targett was able to feel the right ureter to be thickened. On examination, the right kidney could be felt to be enlarged, and was tender on palpation. The left kidney could not be felt. Per vaginam, the lower end of the ureter could be distinctly felt to be thickened. Frequency of micturition amounted to every two hours by day and four

times by night. There were no abnormal physical signs in the thorax. Urine, acid; 1014; albumen present. Pus and red blood discs present in small numbers. Tubercle bacilli were found in the centrifuged deposit.

March 8th, 1905. *Cystoscopy.* Bladder held 8 ounces comfortably. The fundus, anterior and left walls of the bladder were normal. The mucous membrane of the right side and right trigonal area was congested, and just above and outside the right ureteric orifice were a few scattered submucous tubercles. The right orifice was drawn up into a conical contraction, was enlarged and patent, and from it some flakes of muco-pus were emitted in slow efflux. The left orifice was normal, and urine was seen to flow from it in good jets. *Segregation* (March 12th) after a copious drink of hot tea. Urine drawn off from bladder contained 4 grns. per ounce of urea. Urine ran fairly continuously from left side; clear, containing $3\frac{1}{2}$ grns. per ounce urea. From right side only a few drops of turbid urine were obtained in the twenty minutes the examination lasted. The patient remained under observation from March 8th to the 16th, when the consecutive daily total amount of urea excreted amounted to 344, 306, 376, 348, 395, 295, and 360 grains. The specific gravity was fairly constant between 1010 and 1014. April 8th, 1905. Had lost more weight and had more severe right side renal aching. A further consultation was held with Mr. Targett and her husband, who was a doctor, when it was agreed to remove the right kidney and ureter, the left kidney being, from the cystoscopic and segregation tests, shown to be acting, although the specific gravity and total daily urea excreted was small.

April 10th, 1905. *Operation.* Oblique lumbar incision prolonged forwards and downwards in front of iliac spine. Kidney rapidly exposed and drawn up into wound. It was enlarged, and the lower pole was found studded with large discrete tuberculous nodules; whilst on the anterior aspect was a bulging soft fluctuating area as large as a walnut. The ureter was exposed and found much thickened. The renal vessels were cleared, ligatured with plaited silk and divided. The parietal peritoneum was next separated in the lower part of the wound, and the ureter traced down into the pelvis, well below the iliac vessels. It was ligatured and divided, the distal stump being scraped and painted with phenol. The wound was closed with two layers of sutures, with a small drainage-tube in each end of incision. At 11 p.m. patient passed 6 ounces of urine containing 7.5 grns. per ounce of urea. No oozing from wound. The following day she passed 7 ounces of pale urine containing 5 grns. per ounce of urea up to mid-day, but no more was passed during the day. During the next twenty-four hours no urine was passed, and on passing a catheter none was found in the bladder. She was given hot drinks, hot saline enemata and a mixture of tincture of digitalis 10 m. and liquor ammoniæ acetatis 3 drachms four hourly, but no urine was passed. On April 14th patient felt quite well, tongue was clear, pulse 84, and temperature normal. No urine had been passed, but skin was moist and pupils active. There was no pain or tenderness in left renal area. Dr. Hale White saw the patient and suggested diuretin 10 gr. two hourly

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CASE 6.—MRS. J.—Tuberculous abscess of lower pole of kidney, communicating with renal pelvis, which is thickened and studded with tubercles. There are numerous small foci of tubercle, especially in cortical tissue.

for six doses. Intravenous saline infusion, two and a half pints, was also carried out, but followed in half an hour by severe collapse and rigor, with pallor and small thready pulse. Patient was wrapped in hot blankets and given hot brandy and water, which produced profuse perspiration. Sweating continued the greater part of the day. Bowels well opened. April 15th. Patient slept for five hours during night. She had had no sickness, tongue was clean and moist and pupils active. Skin was moist, and she was quite cheerful. Further intravenous infusion of saline, two pints, was given. April 16th. Patient passed about an ounce of pale urine containing a small amount of urea. Skin moist, pulse 84, full volume. Tongue slightly furred. Injection of digitalin, 1/100 grn. given, but patient refused to allow any further saline infusion. April 17th. Vomited twice during night. Pulse 90, tension increased. Tongue slightly dry and brownish. Pupils active. Mental condition quite clear. No urine passed. April 18th. Tongue dry and glazed; some difficulty in swallowing. Skin dry. Some oedema of legs and face. Bowels well open after saline purge. Wound dressed and stitches removed; wound healed primarily. April 19th. More vomiting and patient rather drowsy. Temperature 97.6°. Pulse 94, volume small. No more urine passed. From this time drowsiness increased, breathing became shallow, oedema of legs increased, and patient died on April 23rd. *Post-mortem*. The wound on right side had healed well. There was a small amount of clear fluid in the abdominal cavity. The left kidney was pale, small and fibroid, with some small cysts in the upper pole. There was no deposition of tubercle in any part, and the ureter was normal. Microscopically it showed interstitial nephritis. All the other organs were healthy. In this case the remaining kidney could not yield to the stress of the total urinary excretion after removal of the other, owing to the old-standing nephritis. The tuberculous infection was wholly unilateral, and during the time the patient was under observation previous to operation, it was known that the specific gravity of the urine and the total daily urea excretion was low, but it was decided that the risk of the operation was justifiable considering the bad prognosis without it. The small percentage of urea contained in the urine collected from the left side was thought to be due to the large ingestion of fluid just previously, but probably a colour test would have shown that the renal tissue was inadequate.

CASE 7.—Tuberculous kidney. Left. Nephrectomy and ureterectomy. —S. T., female, æt. 28 years. Patient was sent to me by Dr. Brebner Scott in December, 1907, complaining of attacks of left-sided abdominal pain. No previous illnesses. Three children, youngest (twins) two years old. *History*. For past two years patient has noticed an aching pain in the left side of the back, more or less constant, and made worse by any exertion. On many occasions the patient has had acute attacks of severe spasmodic pain, commencing in the renal angle and passing forwards along the iliac crest into the iliac fossa and groin; it does not reach the vulva or thigh. These attacks have usually followed

some heavy exertion, and last a varying time. At first the attacks caused some faintness, but more recently have become more severe, causing vomiting and shivering. During the attack she has constant desire to micturate, but is unable to pass any urine, and on two occasions (three months and again one month ago) she had passed blood in the urine after an attack of pain. After the severe attack there is prolonged aching in the left renal area. In the intervals between the attacks the frequency of micturition is not increased nor is there any pain during or after micturition. She states that the urine is often turbid and has a faint sediment on standing. She has no cough, but thinks she has lost weight recently. Bowels are very constipated. December 12th. *On examination.* The lower pole of the left kidney can be felt on bimanual examination. It is somewhat enlarged and is distinctly tender. Nothing can be felt in the iliac fossa, but patient complains of tenderness on pressure on the pelvic brim. The right kidney could not be felt. Respiratory system, normal resonance and breath sounds on both sides. Per vaginam, the left ureter can be felt to be thickened; right ureter normal. *Urine*, acid; sp. gr. 1020; small amount of albumen and pus present. Microscopically, pus cells and a few red blood discs present. Cystoscopy. December 18th. *Cystoscopy*, cocaine. Distension 14 ounces. Bladder wall normal except around left ureteric orifice, where it is congested. No tubercles seen. The left orifice is retracted, enlarged and patent, with œdematous lips. Some plugs of muco-pus were seen to be slowly extruded from the orifice. The right ureteric orifice is normal, and clear urine was seen emitted with good efflux. *Segregation.* Luy's separator. Right side, ten drachms of clear urine collected; urea 2.4 per cent. Left side, only three drachms collected in same time. This was purulent and contained tubercle bacilli. December 20th. *Colour test.* A catheter was passed into the right ureter, and 15 minims of 5 per cent. solution of methylene blue were injected into gluteal muscles. The urine collected from the ureteric catheter was coloured a pale green in 35 minutes, increasing to an emerald green in 45 minutes. There was no coloration of the urine from the left side (collected from the bladder) in 1½ hours, but it contained colourless chromogen. A radiograph of the left renal area showed no shadow. December 30th. Catheter specimen of urine was examined. It was pale, clouded with mucoid deposit; acid in reaction; sp. gr. 1016; albumen present. After centrifuging pus, red blood discs and tubercle bacilli were found present.

January 1st, 1908. *Operation.* Oblique lumbar incision and muscles divided. Kidney drawn up into wound, and found enlarged by several soft fluctuating prominences which, on incision, were found to contain thin purulent fluid, and to be lined by sloughing tuberculous granulation tissue. The upper part of the ureter was found much thickened and infiltrated. The renal vessels were separated from the renal pelvis, ligatured and divided. The incision was prolonged downwards, and the peritoneum stripped off the iliac fossa. The ureter was separated well down below the pelvic brim, under the base of the broad ligament, and divided between two catgut ligatures, the distal stump being

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CASE 7.—S. T.—Tuberculous cavities in lower pole of kidney, communicating with the pelvis, which is much thickened. The central portion of the kidney shows a diffuse deposit of tubercle in both medulla and cortex, with numerous small caseous points.

scraped and painted with phenol. The wound was sewn up in a double layer for the muscles, with a small drainage-tube at each extremity of the incision. During the week after the operation patient was very comfortable, but her temperature was constantly raised from 99° to 101° until the eighth day, after which it remained normal. The daily amount of urine passed was successively 15, 34, 40, 42, 57, 45 and 55 ounces. On January 14th the urine was acid; sp. gr. 1020; and contained no albumen, pus nor tubercle bacilli. On February 6th the urine was clear; acid; sp. gr. 1016; and contained no albumen. In September, 1908, the urine was clear and free from albumen. Frequency of micturition amounted to four times during the day and patient was not disturbed at night. She had no pain and had put on weight. December, 1909. Patient is apparently quite well. No pain or increased frequency of micturition. Urine clear; sp. gr. 1018; and free from albumen. In March, 1910, patient seemed quite well. Frequency of micturition amounted to four times in the day and not at night. No pain of micturition, and urine was free from pus or albumen. In July, 1910, the patient was not so well. Had lost weight, and was troubled with cough. No physical signs of pulmonary tuberculosis could be discovered. She was three months advanced in pregnancy. No urinary symptoms.

CASE 8.—Tuberculous kidney. Nephrotomy, followed, in five months, by nephrectomy.—W. C., male, aet. 37, was admitted under my care in April, 1909, for renal pain and lumbar fistula. *History.* The right testicle was removed in 1902, as the result of an injury. In August, 1908, he was admitted into the Cosmopolitan Hospital in Venice for aching in the left loin, increased frequency of micturition, and the presence of pus in the urine, his symptoms dating from a strain in lifting a weight four weeks previously. At this time the left testicle was swollen and painful, but there was no evidence of gonorrhoeal infection. The lumbar symptoms increased, and on November 7th, 1908, the left kidney was explored by Dr. Giordano. Several small abscess-cavities were found in the kidney, but the condition did not warrant removal of the organ, which was drained. The contents of one of the abscesses was examined under the microscope, but no tubercle bacilli were found. For a few days the patient's condition remained very critical, but he was about again at the end of December. Early in January his pain increased, and there was much more discharge from the sinus, but the urine gradually became clearer, though varying from day to day (per letter from Dr. van Someren). Since this time the lumbar sinus has remained open, discharging thin pus and a little urine. During February three small brown stones were passed by the fistula without pain. On admission on April 1st, 1909, he was found to be a thin, but healthy-looking man. He complained of a constant aching pain in the left renal area and of an occasional aching in the right loin. No history of any acute attacks suggesting renal colic. In the upper end of the scar in the left loin is a sinus, discharging thin pus with an urinary odour, and admitting a probe in a slightly backward direction for two and a half inches.

No calculus felt. Pressure over the left kidney and along the course of the ureter causes pain, but no enlargement of the kidney nor swelling of the ureter could be felt. The right kidney could be felt movable and slightly enlarged. Frequency of micturition amounts to every 1—2 hours in day and 2—3 times in the night. He has no pain during or after micturition, and has never noticed hæmaturia. The right testicle is absent, the left shows no evidence of disease. Per rectum, prostate and vesicles were felt to be normal. Neither ureter could be felt. Urine, contained small pieces of muco-pus; acid; sp. gr. 1017; urea 2 per cent. There was no albumen; a small deposit of pus, but no tubercle bacilli could be found. The lungs and heart were normal. April 14th. The urine has been examined on four occasions for tubercle bacilli, but none found. It remains of sp. gr. 1014—1016; urea 1.6 per cent.; and contains a small deposit of pus. A radiograph of the left renal area showed a small irregular shadow, which was again present in a second negative a few days later. Dr. Nolan expressed the opinion that this shadow might be a stone or a tuberculous focus. No shadow seen in ureteric or right renal area.

April 16th. *Examination under anæsthetic.* The bladder was soon washed clear and distended with 14 ounces easily. On *cystoscopy*, both ureteric orifices were normal, and urine flowed from each with fair efflux. The ureteric orifices and bladder wall were normal. An attempt to catheterise the right ureter failed. An injection of methylene blue was made into the gluteal muscles, and Luy's separator was passed. The urine was found to flow more rapidly from the left side than from the right, but neither urine showed any coloration thirty minutes after the injection of the dye. On boiling each with acetic acid, an olive green colour was obtained from the urine of the right side, but no coloration from that of the left side. The separation was continued for an hour, but no coloration appeared in the urine of either side. The urine from the right side contained 1.7 per cent. of urea, that of the left, 1.3 per cent. Per rectum under the anæsthetic both ureters felt normal. By these means, the functional activity of the right kidney remained undetermined, and the risk of operation was put before the patient. This he accepted, and it was determined to open the abdomen first to ascertain the condition of the kidney.

April 20th. *Operation.* Laparotomy through the right semilunar line. The right kidney was found to be enlarged and movable. It was smooth and regular, the pelvis was not dilated or thickened, and it was deemed a functional organ. The left kidney was small, scarred, and uneven, firmly fixed to the abdominal wall. The wound was sewn up in layers, and the patient turned into the lateral position. A probe was passed into the fistula which, with the scar of the previous operation, was enclosed in an elliptical incision. The muscles were divided and the margin of the erector spinæ incised. The kidney was found to be densely adherent to the parietes. On separating the tissues forward, the peritoneum was accidentally opened in the cicatricial tissues and united with thread. On further dissection, the renal capsule was found to be so densely matted in the scar of the previous operation, that

it was impossible to separate the kidney; the capsule was then incised, and the kidney was found to contain numerous softened tuberculous foci, containing caseous pus. The disease was distributed through the scarred kidney, some of the foci measuring three-quarters of an inch in diameter. The organ was removed by subcapsular nephrectomy, the wound partially sewn up by salmon-gut sutures and the remainder packed with gauze. The kidney removed showed numerous areas of tuberculous foci in the lower and median portions, which showed typical tuberculous formation under the microscope. The upper pole of the kidney and the pelvis were free from disease, and the pelvis did not appear to have been opened at the previous operation. Except for some bleeding from the wound requiring further packing, the patient did well. On successive days after the operation he passed 32, 27, 27, 37, 52 ounces of urine. On May 22nd the wound had almost healed, pain had disappeared, urine contained no albumen nor pus, and the frequency of micturition was normal. In July, 1909, the patient reported himself quite well. He was then working in Newcastle, and I have been unable to obtain any further details of him.

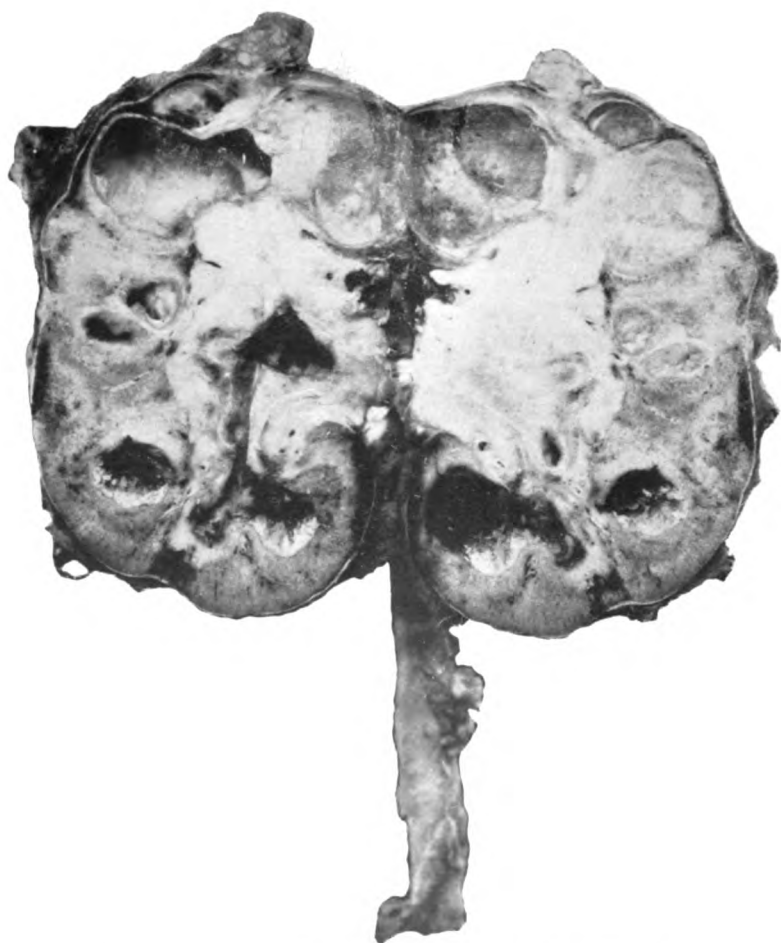
CASE 9.—Renal Tuberculosis. Early vesical infection. Nephrectomy and ureterectomy.—Mrs. E. M., æt. 28, was sent to me by Dr. Bruce Porter on March 3rd, 1909, for increased frequency of micturition, with the following history:—She was always healthy, was married in January, 1907, and went out to Buenos Aires. She remained well until July, 1907, when she first noticed increased frequency of micturition, unaccompanied by pain or hæmaturia. She was relieved for a time by medicine. During the following months the patient was pregnant, during which time the frequency of micturition was further increased, but there was never hæmaturia. Since the birth of the child in February, 1908, the condition remained, with occasional attacks of pain in the right loin. The severity of her symptoms have varied, the frequency of micturition varying from three-quarters of an hour to two hours day and night, but recently the lumbar pain has been constant and more severe, with frequent recurring attacks of renal colic. She has not lost weight in the last year. In Buenos Aires the patient was under the care of Dr. Halahan, who wrote as follows: "There have been symptoms of cystitis for over a year. The urine contains pus, is clouded, and with a small amount of albumen. The urine from the right kidney alone has these characteristics, that from the left kidney being clear and free from albumen, except on the occasion when it proved to be highly albuminous. Installations of silver nitrate, perchloride of mercury, and potass. permanganate produced but temporary benefit. The tubercle bacillus was found in the urine, and an inoculated guinea-pig died from disseminated tuberculosis. The right ureter is easily palpable in the vagina. She has a floating kidney, apparently slightly enlarged, but quite painless." Dr. Halahan thought the right kidney was not diseased, and looked upon the case as one of tuberculous cystitis. He did not advise operation, but climatic treatment together with vaccine injections. *On examination.* The patient is a

healthy-looking person. She complains of constant aching pain in the right loin, with attacks of acute pain radiating from the loin to the inguinal region. Frequency of micturition is increased to $1\frac{1}{2}$ —2 hours by day and about 4 times at night, although at times she has to pass water as often as 8 times during the night. She has never noticed any blood in the urine; there is perineal pain after micturition. There is tenderness on pressure in the hypogastric region, causing a sensation of a desire to micturate; there is also tenderness on pressure in the right loin, where the kidney can be easily felt to be enlarged; it is slightly movable. The left kidney cannot be felt. Per vaginam, the right ureter is readily palpable as a firm, thickened cord in the right fornix. The left ureter was small and normal. Urine, faintly acid; sp. gr. 1012; pale and cloudy, with heavy white deposit of pus. No blood present. Urea 1·2 per cent. No tubercle bacilli were found present in the specimen examined. Dr. Bruce Porter examined the patient and was unable to find any abnormal physical signs in the lungs, or any other lesion outside the urinary tract.

March 10th. *Cystoscopy*—cocaine. Distension 7 ounces. There is a patch of congested and oedematous mucous membrane on the right lateral aspect of the bladder. No ulceration and no submucous tubercles seen. Remainder of bladder wall normal. Right orifice—a large, oval, patent orifice, displaced upwards and outwards, with thick rolled edges. Congested. No efflux of any kind seen from it. Left orifice—small with thin edges. Vigorous efflux of clear urine. *Segregation*. No urine collected from right side in twenty minutes. In same time clear urine collected from left side containing no pus nor albumen. Urea 1·7 per cent. (The morning specimen contained urea 1·7 per cent. with a small deposit of muco pus.) March 12th. *Colour cystoscopy*. At 12.30 p.m. an injection of 15 minims of a 5 per cent. solution of methylene blue was given into the gluteal muscles, and the urine drawn off. In twenty-five minutes the urine was again drawn off, and found of a marked olive green colour, which after extracting with chloroform and boiling the cleared urine with acetic acid, became of a pale prussian blue colour. On cystoscopy, the urine from the left side in thirty-five minutes was distinctly green in colour, in good jets, whilst from the right was a steady trickle of urine containing plugs of muco-pus. March 14th. Three examinations of the urine for tubercle bacilli have failed to reveal their presence. The opsonic index to tubercle (human) was found to be ·56. Daily excretion of urea averages 350 grains. An injection of tuberculin vaccine was given in order to raise the opsonic index preparatory to any operative measure. It was proposed to remove the right kidney and ureter, and the various examinations had shown the left kidney to be acting well and to be apparently unaffected.

March 19th. *Operation*. An incision was made in the lumbar region parallel to the last rib on the right side, and the muscles divided. The renal fascia was opened, and numerous perinephric adhesions found, especially in the upper and posterior aspect. These were divided and the kidney brought up into the wound. It was found enlarged and to present a marked thin-walled, fluctuating cavity the size of a walnut in the upper pole, together with several smaller areas of softening. The ureter was exposed

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CASE 9.—Mrs. M.—Several caseous tuberculous abscesses in kidney. Renal pelvis thickened and tuberculous. Abscess in lower pole communicating with pelvis.

and found much thickened. The tissues around the renal pelvis were separated and the renal vessels isolated, ligatured and divided. The lumbar wound was temporarily closed with Lane's forceps upon the muscle edges, and the patient turned to the dorsal position. A second incision was made in the inguinal region parallel to Poupart's ligament, and the muscles divided. The parietal peritoneum was raised from the iliac fossa and the thickened ureter separated down into the pelvis beneath the broad ligament, clamped and ligatured. After division the ureteric stump was scraped and painted with pure phenol. The divided end of the ureter was wrapped in gauze and drawn up with the kidney through the lumbar incision. The two incisions were sewn up in layers with a drainage-tube in each. The operation of an hour and a quarter was well borne. March 20th. Fairly comfortable night. Urine, 22 ounces; sp. gr. 1022; good colour; urea 11 grains per ounce. March 21st. Urine, 42 ounces. Practically clear. Urea 8 grains per ounce. March 22nd. Can hold urine 4—5 hours. Urine, 71 ounces. Both tubes removed. March 26th. Going on very well. Can hold 10 ounces of urine in bladder. Urea averages 400 grains per diem. March 29th. All stitches out and wounds well healed. Urine, no deposit. Only slightest trace of albumen. To recommence tuberculin injections. April 15th. Is now getting up. Frequency of micturition in day four times and once or twice at night. Opsonic index to tubercle 1.2. April 17th. Bladder held 8 ounces comfortably. On cystoscopy the patch of congestion in right lateral wall is less marked and less extensive. The right orifice is now a long slit, with thickened edges, is not displaced, and no movement seen. Left orifice normal, and good jets of clear urine seen from it. Leaving for country to-morrow. August, 1909. Patient has improved markedly. Weight has increased by 1 stone 4 lbs. She has a slight aching pain after exertion in left loin, but no pain on micturition. Frequency of micturition has diminished to four times by day and once at night. Urine clear; sp. gr. 1018; trace of albumen. Few pus cells found, but no tubercle bacilli after centrifuging urine. Both wounds soundly healed, and no weakness on straining. Is returning to Buenos Aires. May, 1910. Letter from Buenos Aires. Patient is still doing very well. Has to get up once at night to pass urine, but is free from pain. No hæmaturia. Has put on weight since return to South America.

CASE 10.—Tuberculous kidney. Vesical infection. Nephrotomy.—Mrs. D., æt. 45, was seen in consultation with Dr. Gootch and Dr. Crofts at Windsor in January, 1909, and the following history obtained. About seven years ago the patient first noticed an occasional aching pain in the right loin. This gradually increased in severity, especially during her pregnancy four years ago, but never with colic. After the pregnancy the pain decreased somewhat, but has never been entirely absent. The pain was fixed to the right subcostal area posteriorly; there was no pain in the left side, and no increased frequency of micturition, but patient states that the urine was occasionally turbid, but never blood-stained. This

condition remained until March, 1908, when patient first noticed increased frequency of micturition amounting to two hourly by day and twice at night, together with urethral pain after micturition, this latter being attributed to urethral caruncle. In March, 1908, patient saw a surgeon, who found in the urine pus and an acid-fast bacillus which was thought to be the tubercle bacillus. Nephrectomy of the right side was advised, but the patient would not submit to operation. Since this time, the symptoms have become gradually increased in severity. On examination, January 31st, 1909, patient was a well-nourished stout woman. Temperature was normal. Frequency of micturition varied from $\frac{1}{2}$ —2 hours in the day and twice at night, and she complained of pain in the right renal area, fixed, constant and aching, and of pain in the urethra immediately following micturition. The urine was acid; sp. gr. 1018; contained pus, but no blood. There was tenderness on pressure in the suprapubic area. The right kidney could be felt to be slightly enlarged and felt nodular at the lower pole. It was not unduly movable. The left kidney could not be felt. Per vaginam, neither ureter was felt to be enlarged.

Cystoscopy—cocaine. Distension 8 ounces easily. To left of fundus was a small shallow tuberculous ulcer with greyish overhanging border, and surrounded by an area of congestion. There were a few scattered submucous tubercles at the fundus. The trigonal area was oedematous, but remainder of bladder wall normal. Right ureteric orifice was enlarged, oval-shaped, with rigid raised edges. Urine from it flowed with slow, faint efflux; ? turbid. Left orifice, edges slightly oedematous, probably from the surrounding congested vesical area. Clear urine flowed from it in good efflux. *Segregation of urines* had to be abandoned owing to pain. Advised right nephrectomy if daily excretion of urea was satisfactory. With the long history of pain and the distribution of the vesical tubercle, a good prognosis was not given, but operation advised to remove the primary focus of disease, and subsequent treatment of the bladder by vaccine injections. February 15th. Tubercle bacilli were found in urine once in five examinations. Average daily secretion of urea amounts to 350—380 grains.

February 23rd, 1909. *Operation.* Lumbar incision and muscles divided. The perineal fat was found firmly infiltrated and adherent to the lower pole of the kidney, the outer surface of which was scarred. The ureter was exposed and found congested, but not thickened. The kidney was brought up into the wound and freely opened by an incision along the convex border in the lower two-thirds, passing into the renal pelvis. In the lower pole a small tuberculous cavity was opened and thick caseous material removed, but the remaining renal tissue appeared so healthy that it seemed unjustifiable to remove the kidney, especially as the ureter was not infiltrated. The patient showed signs of severe shock and circulatory failure during these manipulations, and it was deemed advisable not to proceed to nephrectomy; the cavity was freely scraped and drained, the remaining renal incision being closed with catgut sutures. The parietal incision was closed by a catgut muscle suture and thread for the skin, a drainage-tube leading to the kidney

being brought out at the upper angle of the incision. A hot coffee enema was given at the completion of the operation, and the pulse improved. The disease was not so extensive in the kidney as had been anticipated, and it did not seem justifiable to remove an organ which contained so much healthy tissue, especially as no critical urinary segregation had been obtained. I preferred in this case to scrape and drain the cavity, and later to treat the disease with vaccine. Patient was again examined on December 27th, 1909. The frequency of micturition had decreased to 2—3 hours during the day and once at night. Urine faintly turbid with pus; acid; sp. gr. 1018. Weight had increased by nearly a stone. On cystoscopic examination, the bladder held 8 ounces comfortably without anaesthesia. The greater part of the vesical mucous membrane was normal, but at fundus of bladder was a scarred area showing bands of contraction. To the left of this was a small area of submucous tubercle. The right orifice was larger than normal, but not retracted. Left orifice normal.

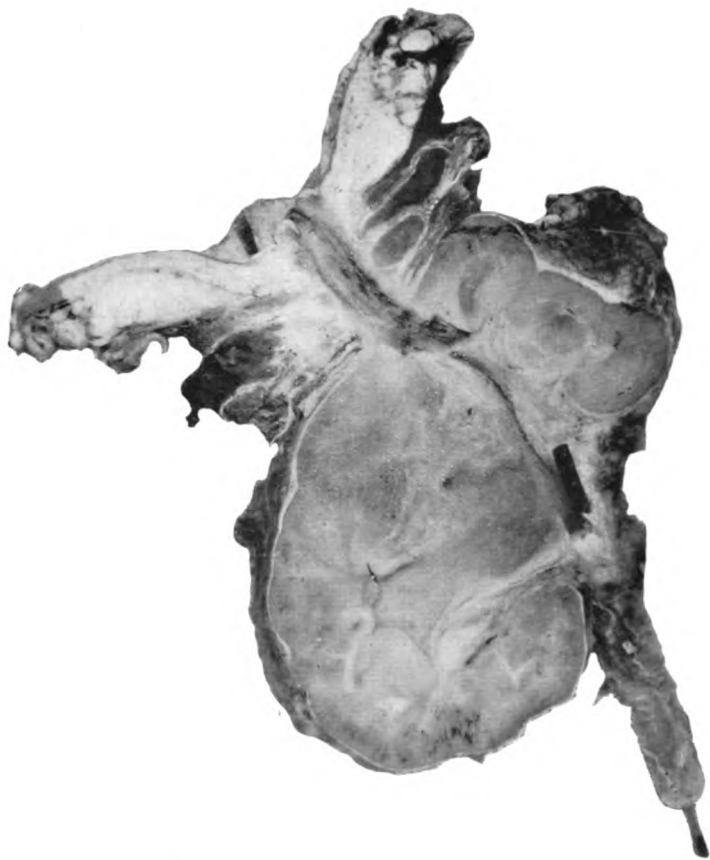
CASE 11.—Renal tuberculosis. Right side. Pyonephrosis opened and drained. Renal fistula. Nephrectomy and ureterectomy.—Rose F., æt. 38, admitted March 1st, 1909. Patient was well until a confinement two years ago, after which she was very ill, and was taken to Fulham Infirmary, where she remained eleven months. During this time she had pain and swelling of the left knee-joint, which was drained, but allowed to become flexed, and subsequently excised by Mr. Pendlebury at the Waterloo Road Hospital. Twelve months ago she commenced to have increased frequency of micturition and aching pain in right lumbar region. This gradually increased in severity, and she was again admitted into Waterloo Road Hospital very ill with a tumour in the right loin, when a large pyonephrosis was opened and drained. In answer to my inquiry, Mr. Pendlebury informs me that the abscess was undoubtedly tuberculous in origin. This operation relieved the pain and frequency of micturition, but a fistula remained, through which urine has been collected by a tube into a bottle. In January, 1909, patient could hold urine without discomfort, and frequency of micturition was normal. During January and February she had difficulty in passing her tube into the renal fistula, which was gradually narrowing, and at the same time causing considerable pain in the right loin. During the time the tube is omitted urine drains from the fistula, and patient is subjected to the constant annoyance of wet clothing. On examination, March 1st, patient was a pale, fallow woman. The left knee-joint had been excised with very good result. She complains of constant aching in the right loin, where there is a scar of a previous operation, together with a small fistula discharging urine. For eight months the urine has been collected into a bottle from this fistula, but recently there has been increased difficulty in passing the tube, together with increased pain in the side. The right kidney can be easily felt below the costal margin. It is very hard, craggy and irregular in shape, somewhat enlarged and tender. The left kidney cannot be felt. Per vaginam, the uterus is anteverted, but

mobile. Neither ureter can be felt to be enlarged. Frequency of micturition is normal. *Urine.* During twenty-four hours the urine collected from the bladder amounted to 28 ounces, and from fistula 20 ounces. The urine from bladder was clear; sp. gr. 1018; acid; and contained no pus nor albumen. Urea 15 grains per ounce. That from the fistula was of turbid, milky appearance. It had a urinous odour, contained pus and urea 2 grains per ounce. No tubercle bacilli could be found after prolonged searches. No adventitious sounds heard in chest.

March 4th. *Cystoscopy*, no anaesthetic. Distension 12 ounces. The bladder wall was pale and normal, and no suggestion of tuberculous deposit found. The left orifice was normal and discharged clear urine in vigorous efflux. The right orifice was a mere pin-point. It showed no sign of vermicular movement, and no urine was seen to be emitted from it. To test the relative functional activity of each kidney further estimations of the daily amount of urea excreted from each organ were made, and it was found that whereas the left kidney excreted an average amount of 350—400 grains in a period of twenty-four hours, the right kidney only excreted from 30—40 grains in the same time. An injection of 15 minims of a 5 per cent. solution of methylene blue was given into the gluteal muscles, and the urine from each side collected at short intervals. It was then found that the urine of the left side was coloured an olive green in half an hour and a distinct emerald green in one hour, with similar gradations in the converted colourless chromagen, whereas the fluid from the fistula showed only the faintest trace of colour in an hour. Hence, it was assumed that the right kidney was almost wholly destroyed, and that the left was uninfected and doing the work of the two, so that a nephrectomy of the right side could be urged with a good prognosis.

March 10th. *Operation.* The old incision was enclosed in an elliptical incision and the muscles divided clear of the old cicatrix. The kidney was exposed after separating old perinephric inflammatory adhesions and found to contain two fluctuating cavities at the lower pole. The pedicle was separated and the vessels ligatured and divided. The lumbar incision was prolonged downwards as far as the outer third of Poupart's ligament, the peritoneum reflected, and the ureter separated into the true pelvis. It was traced under the broad ligament, ligatured and divided, the distal stump being scraped and painted with phenol. The wound was sewn up with a drainage-tube at each angle, the lower leading down to the ureteric stump. There was little shock after the operation. March 11th. Urine, 34 ounces since operation. March 12th. Tubes shortened and patient doing well. Urine, 32 ounces in last twenty-four hours. March 13th. Tubes removed. March 16th. Doing well. Urine, 56 ounces in twenty-four hours. March 19th. Sutures removed, wound well healed. March 29th. Patient up for first time. April 17th. Patient discharged quite well. Urine, acid; sp. gr. 1016; no albumen or pus. Urea, 2.2 per cent. May 3rd. Patient came up for examination. Wound quite healed. No pain of any sort. Urine clear; acid; sp. gr. 1018; no albumen present. August 23rd, 1910.

Primary Unilateral Renal Tuberculosis.



CASE 11.—R. F.—The kidney had been previously drained for tuberculous pyonephrosis. A urinary fistula communicating directly with renal pelvis resulted. Nephrectomy of scarred kidney. Tuberculous foci and tuberculous pyelitis present. The kidney and adherent muscular and cutaneous scar tissue are divided to show the fistula.

Patient quite well. No pain. Urine clear and free from albumen. Scar soundly healed. Frequency of micturition normal. Has increased 10 lbs. in weight.

CASE 12.—Tuberculous kidney and ureter. Nephrectomy and ureterectomy.—C. G. H., male, æt. 29, was sent to me by Dr. Ernest Landon in May, 1909, for increased frequency of micturition. He had noticed that his urine had been turbid for about a year, but he attributed this to the result of urethritis, and took no notice of it. Seven weeks ago he first noticed slight increased frequency of micturition, which has become worse, so that it amounted to every hour and a half by day and four times at night. Recently he has noticed a slight tingling in the glans penis immediately following micturition, and on four occasions has found that the last few drops of urine have been tinged with blood. There has been no pain, either aching or of colic, in the renal areas, and he has passed no stone per urethram. *On examination.* He was a small, thin, anæmic man. There was no pain or tenderness on palpation of the abdomen, but the right kidney could be felt to be enlarged. It appeared to be irregular on the anterior surface, and was tender on pressure; it descended on deep inspiration, but was not unduly movable. The left kidney was not palpable. There were no abnormal physical signs in the chest, the testes were normal, but on rectal examination the right ureter could be felt to be thickened. The left ureter, prostate and vesicles were normal. Urine, acid; sp. gr. 1017; turbid, and contained pus and albumen. Subsequent examination proved the presence of tubercle bacilli. Urea 1·7 per cent. *Cystoscopy*—cocaine. Distension 10 ounces. There was a patch of bright red congestion immediately above and to the outer side of the right ureteric orifice—that is, covering the terminal portion of the right ureter—about the size of a shilling piece. No ulceration or tubercles seen. The right orifice was enlarged and congested, but not retracted. Efflux from it was turbid and of little force. Left orifice normal. Clear urine emitted in good force. June 14th. The left ureter was catheterised for urinary separation. The urine collected from the catheter was clear, and contained urea 1·8 per cent. The urine from the right side obtained at the same time from the bladder was turbid with pus, and contained urea ·8 per cent. A 5 per cent. solution of methylene blue was then injected into the gluteal muscles, after which the urine from the left kidney became distinctly green in 25 minutes, whilst that from the right side was not coloured until 45 minutes had elapsed. The diagnosis of primary renal tuberculosis of the right side was made, and it was determined that the left kidney was functionally active and not infected.

June 29th, 1909. *Operation.* An oblique lumbar incision was made and the muscles divided. The kidney was found to be adherent to the perinephric tissues in the lower pole. These were separated, and the kidney brought up into the wound. The renal vessels were separated from the pelvis, ligatured and divided. The thickened ureter was then separated in its upper four or five inches by stripping up the parietal peritoneum, leaving a fossa into which the kidney was placed. The

lumbar wound was then sewn up by a double layer of sutures, leaving a small drainage-tube in the upper angle. The patient was then turned into the dorsal posture, and a second incision was made in the iliac fossa, parallel to Poupart's ligament. The muscles were divided and the peritoneum raised from the fossa, joining the line of separation from above. The kidney was drawn down from the lower wound and the ureter separated into the true pelvis. The ureter was ligatured as low as possible and divided, the stump being scraped and rubbed with carbolic acid. A small drainage-tube was placed down to the pelvis, and the wound sewn up in layers. The progress of the patient was very interesting. During the fortnight after the operation he passed an average quantity of 44 ounces of urine a day, and both incisions healed by primary union. He had, however, a constantly raised temperature, varying from 100°F. in the morning to 103°—103.6°F. in the evening. He had no pain of any sort, and the frequency of micturition had decreased to almost normal. Dr. Horder saw the patient several times with me, but we were unable to detect any sign of tuberculosis other than at the lower end of the ureter, or any septic infection in the wound. On July 12th a leucocyte count gave a total of 18,800, with neutrophils 83 per cent., hyaline 11 per cent., and lymphocyte 4 per cent. On the following day the urine, which had been previously free from pus, became markedly purulent, coinciding with a fall of temperature to normal. It was thought that an abscess in connection with the lower end of the ureter had ruptured into the bladder. The temperature remained normal, with occasional slight rise to 100°F., but the patient was up on July 20th. On August 3rd a small sinus opened in the posterior wound, but patient seemed quite well. The urine was free from albumen and pus; frequency of micturition was normal, and the patient felt quiet well. He left for the seaside on August 12th. January, 1910. Patient has much improved. Weight has increased by 10 lbs. Frequency of micturition 4—5 times in day; none at night. Urine clear; sp. gr. 1022; free from albumen or pus. August, 1910. Still remains quite well. Frequency normal.

CASE 13.—Tuberculous infection of a kidney partially disorganised by calculus pyonephrosis. Ureteric calculus. Nephrectomy and ureterectomy.—C. C., female, æt. 34, was sent to me by Dr. T. G. Stevens in May, 1909, for increased frequency of micturition. *History.* Two aunts on mother's side died of consumption, and one brother has a "weak chest." The patient has had good health, and of her four children two died in infancy and the surviving two are well. The present illness commenced two years ago, when the patient first noticed slight increased frequency in micturition. This at first lasted a few weeks and then disappeared, to return again after an interval of two months. Since this time the increased frequency of micturition has become more marked, and now (May 22nd) she passes urine about once an hour during both day and night. She has had no pain on micturition, but has noticed a slight aching in the right loin for the last twelve months; there is no history of acute attacks simulating renal colic. The urine for the last year has

Primary Unilateral Renal Tuberculosis.



CASE 12.—C. G. H.—Section of the kidney removed shows two large tuberculous cavities in direct communication with the renal pelvis, which is thickened and studded with tubercles. Smaller tuberculous foci in renal tissues.



been thick, depositing a white sediment on standing, but she has never noticed any hæmaturia. There has been no loss of weight. *On examination.* The patient is a thin, anæmic woman. The right kidney can be easily felt to be enlarged, and is uneven on the anterior surface; the lower pole reaches to the level of the umbilicus, and descends on respiration. The kidney is tender to palpation, and there is marked tenderness on pressure along the abdominal course of the ureter, but the latter cannot be definitely felt. The left kidney is not palpable. Per vaginam, the right ureter can be felt to be distinctly thickened, and was markedly tender to pressure; the left ureter was normal. No adventitious sounds are heard in the respiratory system, but there is a soft systolic bruit heard over the apical region of the heart. *Urine* is turbid; alkaline, with a heavy deposit of phosphates; sp. gr. 1020; pus and albumen present. Urea 1·7 per cent. Tubercle bacilli were found in the urine at a later date. May 25th. *Cystoscopy* under anæsthetic. Distension 6 ounces. There was generalised cystitis, especially over the right basal area, but no evidence was seen of tuberculous disease. The right ureteric orifice was much retracted; no efflux of urine was seen from it. The left orifice was normal, and clear urine was seen to be emitted with good efflux. Catheterisation of the left ureter failed owing to bleeding from the vesical mucous membrane. An intramuscular injection of a 5 per cent. solution of methylene blue was given on the following day. The mixed urine of the two sides was collected by catheter, and showed a faint green coloration in half an hour, increasing to an emerald green in one hour. The converted colourless chromagen showed a grass-green coloration in half an hour, and a deep bluish green in one hour. The patient was kept under observation, when it was found that the daily quantity of urea passed only averaged from 280 to 300 grains per diem. It was explained to her that removal of the kidney was attended with some risk in her case owing to the lowered urea elimination, and the patient decided to have no operation performed. On August 9th she was again admitted under my care. Since her discharge in June the patient has had more severe pain in the right loin, together with suprapubic pain and frequency of micturition increased to half-hourly by day and night. In addition to this, the patient was about three months advanced in pregnancy, and after a consultation it was decided that this must be terminated. Accordingly artificial abortion was induced. August 20th. Since patient has been in hospital the daily excretion of urea has averaged 350 grains per diem. The other symptoms remain unchanged, and the patient is now anxious to undergo operation owing to the increase of pain and to the constant desire to micturate.

August 24th, 1909. *Operation.* The kidney was exposed by the lumbar incision, and found to be markedly cystic, enlarged and tense, there being only a small amount of renal tissue remaining. The ureter was exposed, and found to be very distended, tortuous and thin-walled. The kidney was deemed functionless, but the ureter was quite unlike the usual infiltrated duct found in tuberculous disease, rather than found in cases of ureteric obstruction. The renal vessels were ligatured and divided, and the ureter separated downwards towards

the iliac fossa by stripping off the parietal peritoncum. The kidney was tucked into the bed thus formed, and the incision closed with a single layer of interrupted salmon-gut sutures after providing drainage. An incision was then made parallel to and above Poupart's ligament and the muscles divided. The peritoneum was raised from the iliac fossa, and the ureter again defined and traced upwards to the previous line of separation, the kidney being again exposed and delivered from the iliac incision. The ureter was then traced downwards into the pelvis; during the manipulation the peritoneum was torn and had to be sutured with thread. The pelvic portion of the ureter was dilated to the size of the forefinger, with thinned walls, and so it was decided to explore it before ligaturing it. Accordingly the fossa was packed with gauze, and a small incision made in the ureteric wall; on passing a probe down the ureter a stone was felt in the terminal portion. This was pushed up from the vaginal fornix and removed with difficulty. The ureter was then ligatured with catgut as low down as possible and removed, the stump being painted with phenol. The wound was irrigated with saline, drained and sutured with a single layer of interrupted salmon-gut sutures. The kidney removed was pyonephrotic, with large distended pelvis, and with little renal tissue. In both upper and lower pole was a rounded cavity, lined with granulation tissue, communicating with the distended pelvis; these cavities, on subsequent microscopical examination, showed the typical appearance of tuberculous disease (Dr. Kettle and Dr. Nicholson). The ureter was not tuberculous. I have little doubt that in this case I felt the stone in the lower end of the ureter, and that I mistook it for the thickened ureter of tuberculous disease (having previously found tubercle bacilli in the urine), but the marked tenderness on vaginal examination should have prevented this error. The marked frequency of micturition, in excess of what would be expected from the vesical condition, is also explained by the presence of a calculus in the terminal ureter. The patient progressed very satisfactorily after the operation, and on September 6th could hold urine for two and a half hours at a time. There was still a small amount of pus in the urine, but she had practically no pain. In January, 1910, the patient had gained 10 lbs. in weight, and had practically no pain on micturition. The left kidney was palpable, but not enlarged or tender. Frequency of micturition amounted to every three hours during the day and twice at night. Urine acid; sp. gr. 1022; clear and free from pus and albumen. She was advised to continue treatment with tuberculin vaccine. August, 1910. Patient continues fairly well. She can hold urine for 3—4 hours in the day, but has to pass it twice during the night. She has no pain on micturition, and the urine is free from pus or albumen. Has increased in weight. To continue vaccine injections.

Primary Unilateral Renal Tuberculosis.



CASE 13.—C. C.—This case is remarkable in that it shows more than one pathological lesion. The ureter is much dilated, thinned, and folded upon itself; the renal pelvis is also very distended, these changes being due to the presence of a calculus in the terminal portion of the ureter, which did not wholly obstruct the passage of urine. The renal tissue is small in amount, but contained a large cavity in the upper and central portion lined by tuberculous granulation tissue and communicating with the pelvis. There was a small cavity in the lower pole, part of which has been removed for pathological investigation. Doubtless the kidney was partially disorganised by calculus disease before the tuberculous infection occurred.

LIST OF CASES.

OWN CASES—PRIMARY UNILATERAL RENAL TUBERCULOSIS.

+ = Symptom present. ... = Symptom not mentioned in the report of the case. — = Symptom stated to be absent.																					
Case.	Sex.	Age.	Side.	Initial Symptom.				General Symptoms.										Cystoscopic Examination.	Segregation.	Treatment.	
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Proluse.	Aching.	Colic.	Inc. Freq.	Tumour.	Pyuria.	Tub. bac. in urine.				Ureter thick.
1. M.M.	F.	...	R.	...	+	+	+	+	—	+	+	+	+	...	Some slight cystitis, and to outer aspect of right orifice, two pale submucous tubercles. <i>Right orifice</i> oedematous, with raised patulous lips; no efflux seen. <i>Left orifice</i> normal; strong efflux of clear urine.	<i>Right side</i> .—Continuous drop flow of turbid purulent urine. <i>Left side</i> .—Rhythmic flow of clear urine; in same time collected double the quantity than from right.	Refused operation; vaccine treatment.

OWN CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.					General Symptoms.								Cystoscopic Examination.	Segregation.	Treatment.		
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Hæm.	Aching.	Colic.	Pain.	Inc. Freq.	Tumour.				Pyuria.	Tub. bac. in urine.
2 A. T.	F.	35	R.	+	+	...	+	+	+	+	+	+	+	+	...	Scattered hemorrhagic tubercles around right orifice; small ulcer at fundus of bladder. <i>Right orifice</i> rounded, patent, and drawn up in conical form; no efflux seen. <i>Left orifice</i> small; vigorous efflux of clear urine.	Urine before examination 2-8 per cent. Sub-urea. <i>Right side</i> .—No flow in 25 minutes. <i>Left side</i> .—Good and rhythmic flow of clear urine; 3-2 per cent. urea; right ureter blocked.	Nephrectomy and ureterectomy. Subsequent vaccine treatment for cystitis.
3 C. E.	F.	31	L.	+	...	+	—	+	+	+	+	+	+	...	Small submucous tubercles on outer aspect of left orifice, and a small shallow ulcer to left of fundus. <i>Left orifice</i> enlarged, horseshoe shape, with rigid thick lips; shreds of mucopus slowly expressed. <i>Right orifice</i> normal; good efflux of clear urine. <i>Colour test</i> after injection of methylene blue into gluteal muscles; coloration of urine on right side seen in 85 minutes; no coloration from left after 1½ hours.	Segregation unsatisfactory	Nephrectomy and ureterectomy. Subsequent vaccine treatment.

OWN CASES—Continued.

Case	Sex.	Age.	Side.	Initial Symptom.				General Symptoms.							Cystoscopic Examination.	Segregation.	Treatment.			
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Profuse.	Aching.	Pain	Inc. Freq.				Tumour.	Pyuria.	Tub. bac. in urine.
4 D.M.	M. 31	L.	+	+	+	...	+	+	+	+	+	...	Small patch of tubercle on left lateral wall. <i>Left orifice</i> rigid, patent, round, with congestion around it; flakes of muco-pus in faint efflux. <i>Right orifice</i> rather large, but not oedematous; clear urine in good jets.	Not done.	Nephrectomy and ureterectomy. Vaccine.
5 C.S.	F. 22	R.	...	+	+	...	+	+	+	+	+	...	Congestion around right orifice, but no tubercles or ulceration. <i>Right orifice</i> slightly patulous; margins oedematous; no flow seen. <i>Left orifice</i> normal; strong efflux of clear urine. <i>Colour cystoscopy</i> .—Indigo carmine injected into gluteal muscles; coloration of left urine in 25 minutes; no colour of right in 2 hours.	<i>Right side</i> .—24 c.c. of turbid opalescent urine containing .8 per cent. urea, pus, few blood discs and tubercle bacilli. <i>Left side</i> .—32 c.c. of clear urine; no pus; 1.8 per cent. urea.	Nephrectomy and ureterectomy. Vaccine.

Small patch of tubercle on left lateral wall. *Left orifice* rigid, patent, round, with congestion around it; flakes of muco-pus in faint efflux. *Right orifice* rather large, but not oedematous; clear urine in good jets.

Congestion around right orifice, but no tubercles or ulceration. *Right orifice* slightly patulous; margins oedematous; no flow seen. *Left orifice* normal; strong efflux of clear urine. *Colour cystoscopy*.—Indigo carmine injected into gluteal muscles; coloration of left urine in 25 minutes; no colour of right in 2 hours.

Right side.—24 c.c. of turbid opalescent urine containing .8 per cent. urea, pus, few blood discs and tubercle bacilli. *Left side*.—32 c.c. of clear urine; no pus; 1.8 per cent. urea.

Nephrectomy and ureterectomy. Vaccine.

Nephrectomy and ureterectomy. Vaccine.

OWN CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.					General Symptoms.							Cystoscopic Examination.	Segregation.	Treatment.				
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Hæm.	Pain		Inc. Freq.	Tumour.				Pyuria.	Tub. bac. in urine.	Ureter thick.	Skidgraph.
												Protuse.	Aching.									
6 Mrs. J.	F.	35	R.	+	+	...	+	+	—	+	+	+	+	+	...	Few scattered submucous tubercles above and outer side of right ureteric orifice. <i>Right orifice</i> drawn up into conical contraction, patent, rigid; flakes of mucus in faint efflux. <i>Left orifice</i> normal; clear urine in good jets.	Urine drawn off = 4 grs. per oz. urea. <i>Left side.</i> —Good flow of pale urine, 3½ grs. per oz. urea. <i>Right side.</i> —Only a few drops of turbid urine in 20 minutes.	Nephrectomy and ureterectomy; suppression of urine and death.	
7 S. T.	F.	28	L.	+	—	+	—	+	+	+	+	+	—	No tubercles seen in bladder; slight congestion around left orifice. <i>Left orifice</i> enlarged with patulous oedematous lips; turbid urine in sluggish efflux. <i>Right orifice</i> normal; good efflux of clear urine. <i>Colour cystoscopy.</i> —Methylene blue injected; coloration of urine of right side in ¼ hour, but none of left side during 1½ hours.	<i>Right side.</i> —3x. clear urine; 2.4 per cent. urea. <i>Left side.</i> —3iii. turbid urine containing pus and tubercle bacilli.	Nephrectomy and ureterectomy. Vaccine.	

OWN CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.				General Symptoms.										Cystoscopic Examination.	Segregation.	Treatment.	
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Profuse.	Aching.	Colic.	Inc. Freq.	Tumour.	Pyuria.	Tub. bac. in urine.				Ureter thick.
8 W.C.	M.	37	L.	+	...	+	...	+	...	—	—	+	—	—	+	—	+	+	Bladder wall normal. Both orifices normal, and urine in good efflux from each. <i>Colour test</i> .—No coloration of urine from either side in 60 minutes.	Urine slightly more rapidly from left side. Urea on right side 1.7 per cent., and on left, 1.3 per cent.	Subcapsular nephrectomy after exploratory laparotomy.
9 E.M.	F.	28	R.	+	...	—	—	+	+	+	+	+	+	...	Patch of congestion in right lateral wall; no ulceration or submucous tubercles. <i>Right orifice</i> large, oval, and patent, displaced upwards and outwards; edges thick; no efflux seen from it. <i>Left orifice</i> normal. Vigorous efflux of clear urine. Distension 3vii. No anæsthetic. <i>Colour cystoscopy</i> .—Urine from left side distinctly green in 25 minutes. From right side a trickle of muco-pus.	Mixed urines; urea 1.7 per cent. deposit of mucus and pus. <i>Left side</i> , clear urine; urea 1.7 per cent.; no pus or albumen. <i>Right side</i> , nil in 20 minutes.	Nephrectomy and ureterectomy. Subsequent vaccine treatment.

OWN CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.						General Symptoms.						Cystoscopic Examination.	Segregation.	Treatment.					
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Protuse.	Hæm.	Aching.	Colic.	Pain.				Inc. Freq.	Tumour.	Pyuria.	Tub. bac. in urine.	Ureter thick.
10	F.	45	R.	+	+	—	+	+	+	+	3viii. easily. To left of fundus is a small shallow tuberculous ulcer with few scattered sub-mucous tubercles around it; rest of bladder wall pale. <i>Right orifice</i> large, oval, with raised edges; urine in slow efflux; ? turbid. <i>Left orifice</i> , clear urine in good stream. Edges slightly oedematous.	Not done.	Nephrotomy and drainage of small focus. Vaccine.
11	F.	38	R.	+	+	—	—	—	—	—	—	—	...	After nephrotomy, 3xii. distension. Bladder wall normal; no tubercles seen. <i>Left orifice</i> normal and discharging clear urine in vigorous efflux. <i>Right orifice</i> mere pin-point. No efflux and no contractions. <i>Colour test</i> —Urine from left side stained emerald green in 40 minutes after injection of methylene blue; no colour in right urine.	From bladder.— <i>Urine</i> , clear, acid; urea 15 grs. per oz.; no pus. From <i>fistula</i> , turbid milky fluid; pus present; urea 2 grs. per oz.	Nephrotomy, followed by nephrectomy and ureterectomy.

GUY'S HOSPITAL CASES.—PRIMARY UNILATERAL RENAL TUBERCULOSIS.

+ = Symptom present. ... = Symptom not mentioned in the report of the case.
 — = Symptom stated to be absent.

Case.	Sex.	Age.	Side.	Initial Symptom.					General Symptoms.						Cystoscopic Examination	Remarks.				
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Profuse.	Aching.	Pain.	Colic.			Inc. Freq.	Tumour.	Pyuria.	Tub. bac. in urine.
1	F.	43	R.	+	..	+	+	..	+	+	Nephrotomy. Numerous tuberculous cavities.
2	M.	30	L.	+	+	+	+	+	+	+	Declined operation.
3	M.	26	R.	+	+	+	+	+	+	Nephrectomy.
4	F.	42	L.	..	+	..	+	+	+	+	+	+	Segregated urine :— R.=1·8 per cent. urea ; L.=·5 per cent. urea. Nephrectomy.
5	F.	—	R.	+	+	+	..	+	+	Nephrectomy.
6	M.	7	L.	+	..	+	+	+	+	+	+	No operation.
7	F.	43	L.	+	+	+	+	+	+	Segregation. Normal urine from R.; nil from L. Nephrectomy.

GUY'S HOSPITAL CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.					General Symptoms.								Cystoscopic Examination.	Remarks.			
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Profuse.	Aching.	Pain.	Inc. Freq.	Tumour.	Pyuria.			Tub. bac. in urine.	Ureter thick.	Skiagraph.
8	F.	27	L.	+	..	+	+	+	+	..	+	Cystitis. Too extensive for operation.
9	F.	19	L.	+	+	Bladder and orifices normal.	Nephrectomy and ureterectomy.
10	M.	6	L.	+	+	Nephrotomy.
11	M.	30	R.	+	+	+	+	Nephrotomy; subsequent nephrectomy.
12	F.	54	R.	+	+	+	+	+	No operation.
13	F.	36	R.	+	+	+	..	+	Nephrectomy.
14	F.	27	R.	+	+	+	+	Right orifice retracted. Left orifice normal. Some tuberculous cystitis.	Refused operation.	
15	F.	13	R.	+	+	+	+	Pus from right ureter. Small ulcer close to orifice.	Large pyonephrosis. Nephrectomy. Tubercle bacilli in renal pus.
16	F.	25	R.	Peritoneal.	+	+	+	Right orifice edematous. Left orifice normal.	Nephrectomy and ureterectomy.

GUY'S HOSPITAL CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.					General Symptoms.							Cystoscopic Examination	Remarks.			
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Hæm.		Pain.		Inc. Freq.	Tumour.			Pyuria.	Tub. bac. in urine.	Ureter thick.
17	M.	50	R.	+	+	..	+	+	+	+	Large tuberculous pyonephrosis opened and drained.
18	M.	33	L.	+	+	..	+	Perinephric abscess. Removal of caseous kidney.
19	M.	30	R.	..	+	+	+	+	+	+	+	+	..	Vaccine treatment. Secondary cystitis.
20	F.	40	L.	+	+	+	+	+	+	+	+	+	..	Nephrectomy.
21	M.	33	R.	+	..	+	+	+	+	+	+	+	+	Not satisfactory.	Nephrectomy. Later vaccine treatment for cystitis.
22	M.	20	R.	+	+	+	+	+	+	+	+	+	Bladder trabeculated. No urine from right ureter.	Nephrectomy and subsequent vaccine.
23	M.	47	R.	+	+	+	+	+	+	+	+	..	Nephrectomy and ureterectomy.
24	F.	13	R.	+	+	+	+	+	+	+	+	Pus seen from right ureter.	Nephrectomy.

GUY'S HOSPITAL CASES Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.				General Symptoma.							Cystoscopic Examination	Remarks.				
				Pain.	Collc.	Pus.	Blood.	Frequency.	Tumour.	Hæm.		Pain.		Inc. Freq.			Tumour.	Pyuria.	Tub. bac. in urine.	Ureter thick.
25	F.	29	L.	+	+	+	+	+	+	+	+	+	Unsatisfactory.	Nephrectomy and ureterectomy. Cystitis; vaccine.
26	M.	37	L.	+	+	+	+	+	Nephrectomy. Kidney cretaceous and functionless. Pain referred to other side.
27	F.	35	L.	..	+	+	+	+	+	+	+	+	+	..	No operation. Marked tuberculous history.
28	F.	31	L.	..	+	..	+	No operation.
29	M.	30	R.	..	+	+	Small tuberculous ulcers around right orifice. <i>Left orifice</i> normal.	Previous renal exploration; nil found. Symptoms continued. Nephrectomy.
30	M.	38	R.	+	Tuberculous perinephric abscess.

GUY'S HOSPITAL CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.					General Symptoms.							Cystoscopic Examination	Remarks.				
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Hæm.		Aching.	Pain.	Inc. Freq.	Tumour.			Pyuria.	Tub. bac. in urine.	Ureter thick.	Skia-graph.
										Slight.	Profuse.										
31	F.	51	R.	+	+	..	-	..	+	Small ulcer at side of right orifice; urine from it in slow efflux.		
32	F.	37	R.	+	+	..	+	+	..	-	Cystitis on right side. No tubercles or ulcer. <i>Right orifice</i> dilated. <i>Left orifice</i> normal.	Segregation. Clear urine from left side. Right urine in smaller quantity, and purulent. Vaccine treatment.	
33	F.	44	L.	+	+	+	+	+	+	+	Colic caused by passage of pieces of muco-pus. Refused operation. Vaccine treatment.		
34	F.	30	R.	+	+	..	+	+	+	+	+	..	Nephrectomy after examination of left kidney by laparotomy.		
35	M.	24	-	+	+	-	+	+	+	+	Early tuberculous epididymitis. Refused operation.		

Primary Unilateral Renal Tuberculosis.

99

Gray's Hospital Cases--Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.					General Symptoms.										Cystoscopic Examination	Remarks.		
				Pain.	Collc.	Pus.	Blood.	Frequency.	Tumour.	Hæm.		Pain.		Inc. Freq.	Tumour.	Pyuria.	Tub. bac. in urine.	Ureter thick.			Skia-graph.	
										Slight.	Profuse.	Aching.	Collc.									
36	F.	6	L.	+	+	+	Large perinephric abscess. Child very ill, and opened by rib resection. Died of pneumonia. Post-mortem, tuberculous pyonephrosis and perinephric abscess.
37	F.	17	L.	+	+	+	Refused treatment.
38	F.	27	R.	+	+	+	No operation.
39	M.	37	R.	+	+	+	+	Died suddenly before any operation was performed. Right kidney tuberculous.
40	F.	36	R.	+	+	+	+	Right orifice hidden in mass of granulations. No tubercles seen in bladder.
41	F.	26	R.	..	+	+	+	+	Pus seen from a congested right orifice.
42	F.	29	L.	+	+	+	+	Nephrotomy and drainage.
																						Medicinal treatment.

GUY'S HOSPITAL CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.						General Symptoms.								Cystoscopic Examination.	Remarks.		
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Profuse.	Aching.	Colic.	Inc. Freq.	Tumour.	Pyuria.	Tub. Bac. in urine.			Ureter thick.	Skidgrap h.
43	M.	25	L.	+	..	+	..	+	+	..	+	+	+	+	Large tuberculous pyonephrosis. Nephrectomy.
44	M.	3	L.	+	+	..	+	+	+	+	Tuberculous renal abscess. Nephrectomy.
45	F.	40	R.	+	+	+	+	+	+	+	+	+	Medicinal treatment.
46	M.	36	R.	+	+	+	..	+	+	+	+	+	No operation.

ST. PETER'S HOSPITAL CASES—PRIMARY UNILATERAL RENAL TUBERCULOSIS.

47	F.	30	R.	+	...	+	...	+	+	+	—	Bladder congested, no tubercles seen. Right orifice "dragged out."	Operation refused.
48	F.	31	R.	...	+	+	...	+	+	+	—	...	+	Right orifice inflamed, enlarged, and dragged upwards.	No operation.

ST. PETER'S HOSPITAL CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.					General Symptoms.							Cystoscopic Examination	Remarks.		
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Profuse.	Aching.	Colic.	Inc. Freq.	Tumour.			Pyuria.	Tub. bac. in urine.
49	M.	32	R.	+	+	..	+	..	+	Blood seen from right ureter. Bladder normal.	Renal focus drained.
50	M.	32	L.	+	..	+	+	+	Tuberculous pyonephrosis drained.
51	M.	30	L.	+	..	—	—	+	—	+	Bladder wall infected, and with oedematous folds. <i>Left orifice</i> , "Golf-hole." <i>Right orifice</i> slit. Clear efflux.	No operation.
52	F.	20	L.	+	..	+	+	+	Left ureteric orifice retracted.	Nephrectomy and ureterectomy.
53	M.	54	R.	+	..	—	—	—	—	+	General cystitis with small ulcer on right side. <i>Right orifice</i> "puckered and rounded." <i>Left orifice</i> normal.	Nephrectomy and ureterectomy.
54	M.	22	L.	+	—	—	+	—	—	..	+	..	<i>Left orifice</i> "dragged out." <i>Right orifice</i> normal.	Nephrectomy and ureterectomy.

ST. PETER'S HOSPITAL CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.				General Symptoms.						Cystoscopic Examination.	Remarks.						
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Profuse.	Aching.	Pain.			Inc. Freq.	Tumour.	Pyuria.	Tub. bac. in urine.	Ureter thick.	Skiagraph.
61	F.	38	R.	+	+	+	+	+	+	+	Congestion of right bladder wall. <i>Right orifice</i> enlarged, reddened, ragged, and irregular, with ring of tubercles around it. Mucopurulent efflux. <i>Left orifice</i> normal. Clear efflux.	Nephrectomy and ureterectomy.
62	M.	16	L.	+	+	..	+	+	+	+	No operation.	No operation.
63	M.	35	L.	+	+	+	+	+	..	Pyonephrosis. Nephrectomy.	Pyonephrosis. Nephrectomy.
64	M.	20	R.	+	+	+	+	+	..	Cystoscopy failed. Thick, caseous areas.	Nephrectomy.
65	F.	37	R.	+	+	+	+	+	..	No operation. Vaccine treatment.	No operation. Vaccine treatment.
66	M.	20	L.	+	+	+	+	..	<i>Left orifice</i> thickened and congested. Mucopurulent efflux.	Refused operation.

ST. PETER'S HOSPITAL CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.					General Symptoms.						Cystoscopic Examination	Remarks.				
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Slight.	Profuse.	Hæm.	Aching.	Pain.			Colic.	Inc. Freq.	Tumour.	Pyuria.
67	M.	54	R.	+	+	..	+	+	+	Tuberculous abscess in upper pole of kidney. Nephrectomy.
68	M.	29	L.	+	+	..	+	+	+	Left ureter drawn up. Nephrectomy.
69	M.	34	R.	+	+	—	+	..	+	..	Right orifice "caked" with ulceration around it. Nephrectomy and ureterectomy.
70	M.	30	L.	+	+	..	+	—	+	..	+	..	Left orifice round, rigid and patulous. Tuberculous ulcer of bladder. No operation.
71	M.	18	L.	..	+	+	+	+	+	Nephrotomy.
72	M.	44	L.	+	+	..	—	—	+	..	—	..	Left orifice dilated. Purulent efflux. Tubercles in bladder. No operation.
73	M.	39	L.	+	+	+	+	+	+	+	+	..	Nephrectomy and ureterectomy.

ST. PETER'S HOSPITAL CASES—Continued.

Case.	Sex.	Age.	Side.	Initial Symptom.				General Symptoms.								Cystoscopic Examination	Remarks.				
				Pain.	Colic.	Pus.	Blood.	Frequency.	Tumour.	Hæm.		Pain.		Inc. Freq.	Tumour.			Pyuria.	Tub. bac. in urine.	Ureter thick.	Skidagraph.
										Slight.	Profuse.	Aching.	Colic.								
74	M.	35	L.	+	+	—	+	+	+	—	+	Nephrectomy.	
75	M.	38	R.	+	+	+	+	+	...	+	Right orifice patulous and drawn up.	No operation.	
76	M.	32	R.	+	+	+	+	+	—	...	+	+	+	Right orifice congested. Purulent efflux. No vesical deposit.	Operation refused.	
77	M.	24	L.	...	+	+	...	+	+	+	...	+	Left orifice cedematous and puffy.	Nephrectomy.	
78	M.	28	L.	+	+	+	+	+	+	...	Left orifice very retracted. Ulceration.	Refused operation.	
79	M.	30	L.	+	+	...	+	—	+	+	+	Left ureter dilated. Vesical ulceration.	No operation.	

THE TREATMENT OF APPENDICITIS.

(BASED ON 545 CASES ADMITTED TO GUY'S HOSPITAL,
1906—1909 INCLUSIVE.)

By

NATHAN MUTCH, B.A.

IN the treatment of appendicitis the co-operation of medicine and surgery is more needed than in that of any other disease. The onset is often so sudden, and the fatal course so rapid, that early diagnosis and prompt action are essential: and as the number of persons (in England and Wales) dying from this complaint in each year is about 2,000, a small diminution in the case mortality would be the means of saving hundreds of lives.

In this paper the following points are discussed, and illustrated wherever possible by the cases of appendicitis treated in Guy's Hospital during the four years 1906—1909.

- A. The great advantages of operation performed within thirty-six hours of the onset of the attack.
- B The treatment of patients not coming under medical observation until two or more days after the commencement of the illness.
- C. The expectant treatment to be adopted whenever immediate operation is impossible.

Before the statistics brought forward can be utilised as a basis for treatment in general, those conditions peculiar to Guy's Hospital practice must be taken into consideration. It is a characteristic of the class from which most of these patients are drawn that small discomforts cause them little or no inconvenience, so that those slight attacks of appendicitis, which are often seen in middle-class practice, are but rarely treated here.

A second result of the hesitation of the Borough patient to seek advice is that many of the severe cases only come under observation in the later stages of the illness, often after the development of general peritonitis.

The outcome of these conditions is that appendicitis, as seen at Guy's Hospital, is a much more severe affection than that met with among the more educated classes, and the mortality is much higher than that obtained by equal surgical skill in private practice.

A. Let us first consider the question of early operation. Even the most conservative physician would advocate this if he could foretell that otherwise general peritonitis would occur. The ideal method would be to operate only when other treatment would not lead to a favourable result. But unfortunately this is quite impossible in so treacherous a disease.

In the first place, there is great disparity between the symptoms and the severity of the attack. Slight abdominal pain and repeated gastric disturbance may herald the development of a large abscess or a virulent spreading peritonitis; whilst a patient may be admitted to the hospital with severe vomiting and intense pain, and yet recover perfectly in a few days without operation.

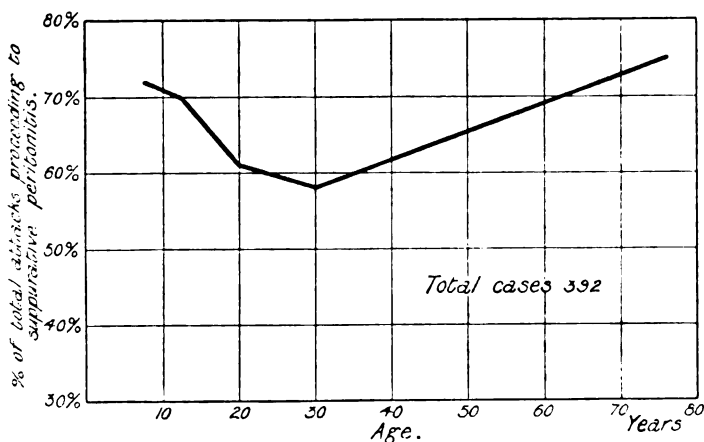
And, secondly, there is "the period of repose." There may be a complete subsidence of severe symptoms, and, although the abdomen may contain a gangrenous appendix or the purulent fluid of a spreading peritonitis, the patient may walk up to the hospital and feel so completely free from trouble that an operation may seem to be redundant. Yet operations performed at this stage will reveal the conditions just described. This is a

very real danger, as was first pointed out by Mr. Symonds of this hospital, and more recently emphasized by Mr. Lockwood, of St. Bartholomew's.

If, then, one cannot rely upon the symptoms to guide one in prognosis, can any help be derived from a consideration of the age and sex of the patient or of the number of previous attacks?

(i) *Age*.—The proportion of cases admitted to the wards, which ultimately require operation for suppurative conditions, either peritonitis or abscess, varies very little with the age of the patient, there being a slightly greater tendency for dangerous septic conditions to develop at the two extremes of life (curve i.).

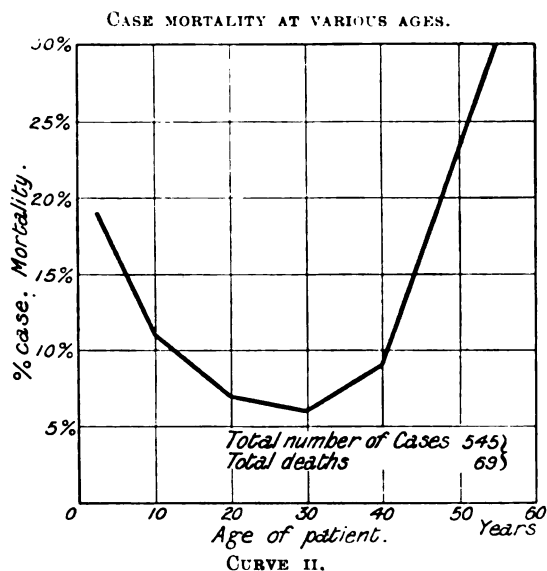
PROPORTION OF ATTACKS WHICH PROCEEDED TO SUPPURATIVE PERITONITIS AT VARIOUS AGES.—(First attacks only.)



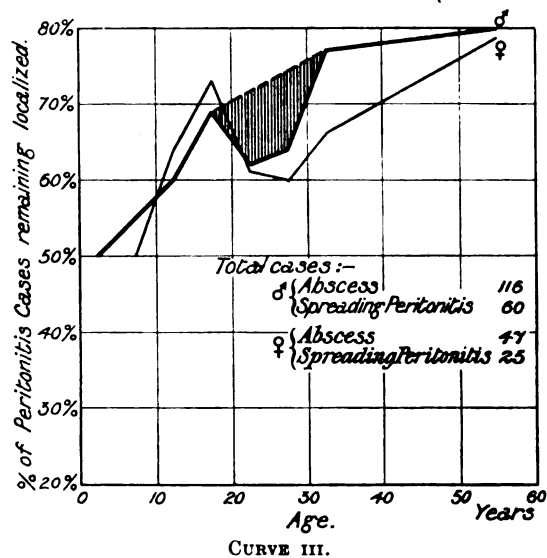
CURVE I.

But if one considers only those cases in which suppuration occurred, then a very interesting relationship is brought out. The percentage of *localised* abscesses increases steadily with the age. This is probably due to the development of an increasing resistance to those pyogenic organisms with which throughout life the body inevitably comes into contact: but whether there is with advancing years any correlated increase in the opsonic index to the organisms concerned, I do not know. The pheno-

menon, however, is very definite. This excessive proportion of spreading peritonitis cases largely accounts for the increased case mortality in early life (curve ii.). There is one irregu-



TENDENCY TO LOCALIZATION IN PERITONITIS CASES.—(First attacks only.)



larity in the curve. Between the ages of 20 and 30 in men and in women there are distinctly more spreading peritonitis cases than one would expect. This is represented by a dip in the curve showing the tendency to localisation with age, and is probably the result of the rupture of well shut-off abscesses; for it is at this age that people learn to ignore small pains and concentrate their energies on wage-earning. Little attention is given to the comparatively slight symptoms which accompany the formation of an abscess, and the patient continues to work and expose himself to trauma until the sudden bursting of the abscess produces a fatal peritonitis (curve iii.).

(ii) *Sex*.—The proportion of cases going on to suppuration is distinctly greater in males than in females, being 70 per cent. for men and 55 per cent. for women.

But suppuration having once occurred the tendency to localisation is about the same in the two sexes, 65 per cent. remaining as well-defined abscesses.

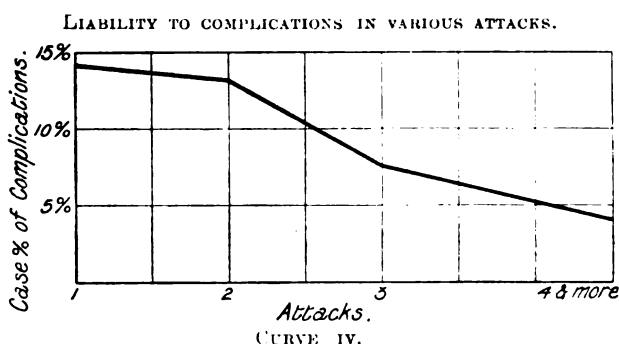
(iii) *Number of Previous Attacks*.—Analysis of the hospital cases indicates that the first attack is usually the most serious one, and that subsequent attacks are, on the whole, of diminishing severity. This is shown in the following ways:—

(a) The tendency for conditions to develop, which render an operation inevitable, diminishes with the number of the attack. This phenomenon is exhibited alike by males and by females (Table P).

(b) In suppurative cases the probability of a peritoneal infection remaining localised increases with each attack. This also can be demonstrated separately for males and for females (Table O).

(c) Both the case mortality and the operation mortality are higher for first than for subsequent attacks (Table B).

(d) The frequency with which complications occur is less for second and later than for first attacks (Table J and curve iv.), although the complication mortality is constant throughout (Table K).



The above considerations indicate that whatever arguments are brought forward in support of early operation refer with especial force to young people, and to males and for first attacks.

Such, then, is the uncertainty of this disease; and if the case is left until clear evidence of severe complications arise, it will be too late to avoid an operation with a high mortality.

In place of this alternation between brilliant recoveries and shocking disasters, what sure uniformity of result can modern surgery offer?

The answer to this question requires the consideration of the consequences of early operation, which may be studied under the following headings:—

(1) *Mortality*.—Sixteen operations have been performed at Guy's Hospital during the first thirty-six hours of the attack, and *no* deaths have resulted.

This appears all the more satisfactory when one remembers that treatment is distinctly conservative, and that the operator is only called in when the symptoms are distressing and the prognosis seems grave. In only two cases was inflammation in the catarrhal stage. An analysis of the conditions found at the operation is as follows:—

Acute catarrhal inflammation	2
Empyema of the appendix...	4
Gangrene	2
Small local abscess	2
Peritonitis spreading from gangrenous appendix	2
Acute perforation	4

Again, 42 operations have been performed during later stages of acute attacks in which spreading peritonitis and abscess were both absent, and *no* deaths have resulted.

Clearly, then, operation in the first thirty-six hours or before severe peritoneal infection has commenced is quite a safe procedure, and its results contrast strongly with those of later operation and expectant treatment.

The total number of operations during acute attacks was 340, and the mortality 20 per cent.

The total number of cases treated was 545, and the mortality 13 per cent.

(2) *Complications*.—These may be divided into two main groups:—

(a) Those which tend to occur most frequently between the third and fifth day. Such as:—

Pneumonia, pleurisy, empyema and other pulmonary affections.

Pericarditis.

Paralytic intestinal obstruction.

Acute ulceration of the gut.

Subphrenic abscess.

(b) Those which increase in frequency as operation is more and more delayed. Such as:

Fæcal fistula.

Portal pyæmia.

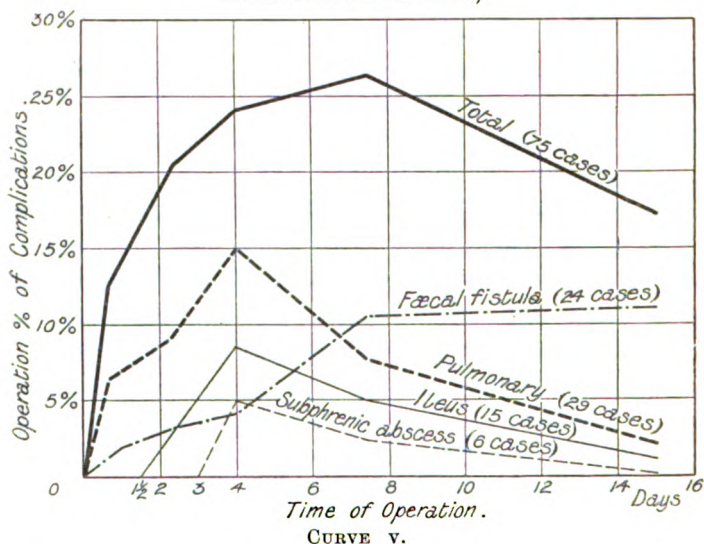
Intestinal obstruction by bands.

No severe complication followed any of the operations performed during the first thirty-six hours. One patient had an attack of bronchitis, whilst in another a small fæcal fistula developed and closed spontaneously four days later; but none of the grave complications occurred, such as intestinal paralysis with a mortality of 75 per cent., portal pyæmia with a mortality of 100 per cent., and subphrenic abscess with a mortality of 85 per cent.

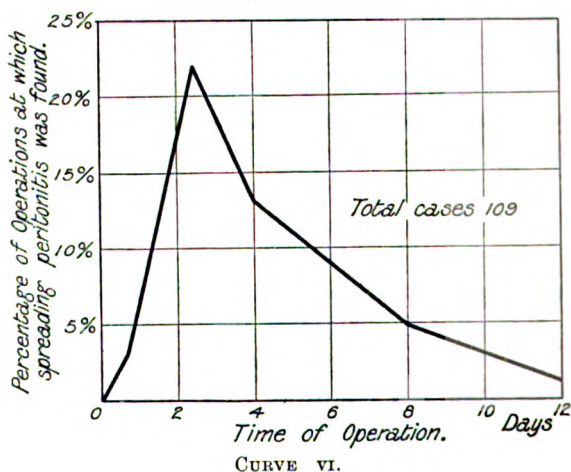
The curves show very clearly how the incidence of acute complications and of spreading peritonitis rises rapidly as the attack

proceeds and that this rise coincides with the increased mortality. So that prompt operation is essential if the dangerous second to sixth day period is to be avoided (Curves v., vi., vii.).

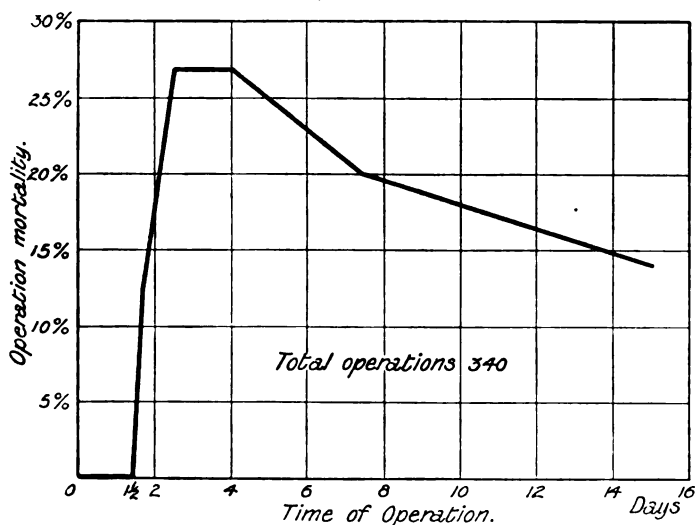
INCIDENCE OF COMPLICATIONS FOLLOWING OPERATIONS AT VARIOUS INTERVALS FROM THE COMMENCEMENT OF THE ATTACK.—(Simple peritoneal infection is not included.)



TIME FROM THE COMMENCEMENT OF THE ATTACK AT WHICH SPREADING PERITONITIS DEVELOPS.



OPERATION MORTALITY AT VARIOUS INTERVALS FROM COMMENCEMENT OF ATTACK.



CURVE VII.

(3) *Expense*.—The early operation involves far less medical and surgical attendance. Repeated operations for residual abscesses, for removal of appendices left in after a hurried incision during the acute attack, for closure of faecal fistulae, and for enterostomy, etc., are avoided.

The actual duration of the illness is greatly curtailed, and the convalescence shortened. The average time spent in the hospital by the various classes of patients was as follows:—

- (a) Those on whom "interval operations" were performed, three weeks.
- (b) Those operated on during the first thirty-six hours, four weeks.
- (c) Those operated on between the third and fifth days, six weeks.
- (d) Those operated on after the tenth day, six weeks.

(4) *Injury to Physique*.—The prolonged absorption of septic materials, which inevitably follows the development of a large appendicular abscess, cannot fail to injure permanently the

health of the patient. The suffering undergone is incomparably greater than in the case of early operations, and chronic invalidism often results.

The disturbance of the intestinal functions is much more lasting, and is aggravated by masses of adhesions, which may at any time produce acute obstruction, and are a constant menace to the patient's life. Spread of infection to the female organs of reproduction is more liable to occur, with resulting sterility.

Another important consideration is the nature of the scar. If the operation is performed early, the drainage may be reduced to a minimum, or dispensed with altogether, so that healing by first intention is the rule; and this, combined with the excellent practice of opening the abdomen through the rectus sheath or by the muscle-splitting method, greatly reduces the probability of a subsequent ventral hernia. But in the later operations incisions are free and their position determined by that of the abscess, whilst long-continued drainage is adopted; so that eventually there is produced a wide gap in the abdominal wall which closes by granulation, and remains a source of weakness and a favourable site for the development of ventral hernia.

Such are some of the great advantages offered by early operation, and by early operation is meant one performed within thirty-six hours of the beginning of the attack, for immediately after this, commences one of the most dangerous periods in the course of the disease.

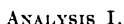
Looking at the question from another point of view, what is the probability that operation will be inevitable in the case of an attack of such severity as to cause the patient to seek admission to the hospital?

Our statistics show that only 36 per cent. recover from their first attack without operation, and, taking into consideration subsequent attacks, only 13·5 per cent. avoid surgical treatment during the acute or quiescent stage, whilst 75 per cent. are operated on during the acute stage.

When one bears in mind the enormous number of cases of appendicitis occurring each year, it does not seem at all sur-

The benefit derived from delay is that 14 of every 100 patients escape without operation of any kind. But the price paid for this is the death of 10 out of every 100 patients and the production of weak abdominal walls and numerous adhesions in 35 others, who recover from suppurative peritonitis. For 10 lives saved and 35 abdominal walls preserved by early operation, the subjection of 14 patients to one of the safest of all abdominal operations involving the loss of an organ of very doubtful value, would be a small price to pay (Analysis I.).

Average course of Appendicitis as treated at Guy's Hospital.



No definite prognosis can be given at the commencement of an attack of appendicitis, but its treatment by operation will be unavoidable in 64 per cent. of the cases.

By operation within thirty-six hours of the onset of the illness the case mortality is reduced to a minimum, and the evil after-results which accompany later operations are almost completely avoided.

B. Unfortunately the medical man does not always see the beginning of attacks, and is often called upon to decide for or against operation on the third day or later. Three groups of cases come under consideration:—

(1) Infection may be localised to the appendix. The operation mortality here is almost negligible, as pointed out previously, whilst an appendix which is still giving trouble on the third day is a source of great danger.

(2) A localised abscess may have formed. The operation mortality for this type is 10 per cent. and does not decrease to any extent with delay in operation. Only 5 per cent. recover spontaneously, whereas the danger that spreading peritonitis will result from rupture into the peritoneal cavity is great. In this case the mortality becomes very high indeed, much higher than for ordinary spreading peritonitis where localisation has never taken place. With the methods of modern surgery the risk of causing a spread of infection is small, and if the primary object be the relief of pus tension, no harm, but much good, must ensue.

(3) The peritoneal infection may be spreading, with or without hope of subsequent localisation. In either, the risk of rapid death is imminent unless the source of suppuration is speedily removed by operation, in which case the mortality is 42 per cent. This figure is the mean derived from a consideration of all cases; if the operation be performed between the thirty-sixth and forty-eighth hours from the commencement of the attack the mortality is only 22 per cent., whilst in the case of operations after the sixth day it becomes 60 per cent.

Where the infection is not widespread the appendix can be removed safely and the site mopped with dry sponges. This procedure involves little risk of mechanical spread of the peritonitis and gets rid of the original focus of the disease. When the peritonitis is very general, failure to operate is invariably followed by death.

The general rule, then, even in these late cases, is to open the abdomen at once, but to modify the nature of the operation to suit the conditions revealed.

Doubtless many, if left, would escape, but when percentages are considered, it is evident that prompt operation will save more lives than will expectant treatment, and this principle must hold good until medicine teaches us how to obtain a clinical classification in agreement with the pathological one.

Treatment is required for all classes of cases and at all periods from the commencement of the attack. To deal with the whole subject in one short paper like the present is impossible, but more feasible, perhaps, is a discussion of such treatment as can be grouped around the various derangements of the intestinal functions which present themselves at all stages of the disease.

(i) The chronic intestinal stasis associated with repeated slight attacks of abdominal pain in the right iliac region. Many of the sufferers date the onset of their constipation from their first attack of pain, whilst others assert that they were constipated long before their pain commenced.

To suit these two classes of patients we find two opposing theories:—

- (a) That the constipation results from the appendicitis;
- (b) That constipation is the cause of appendicitis.

Much may be said in support of either hypothesis, and the Guy's Hospital statistics show that each is probably correct, and that both primary and secondary constipation occur in association with appendicitis. The treatment of such cases must be appendicectomy, combined with general treatment for intestinal stasis.

(ii) Constipation occurring suddenly at the commencement of an attack (more fully discussed in the third part of the paper). This is reflex in origin, and is brought about by irritation in the ileo-cæcal region which inhibits intestinal movements. No treatment is called for; it is part of a beneficial reaction of the body to the appendicular lesion. The condition may persist, and attempts to relieve it in the later stages of an attack are particularly dangerous. Cases in which rupture of a pelvic abscess has followed the needless administration of an enema are not uncommon.

(iii) The paralytic intestinal obstruction which often accompanies an appendicular abscess or spreading peritonitis. Three factors probably combine to induce this condition:—

(a) Inhibition of tone and peristalsis by the splanchnic nerves. Just as peritoneal irritation near the appendix will cause a local inhibition, so general peritonitis will produce universal cessation of intestinal movements.

(b) The toxic effect of the pus which bathes the contents of the peritoneal cavity.

(c) The manipulation of the gut during operation.

Murphy has studied the matter carefully by means of experiments performed on cats, and has shown conclusively that the one factor which is most potent in producing post-operative ileus is the handling of the gut. Anæsthetics, exposure to the air, or very considerable cooling, each have little or no effect, but even gentle manipulation of the bowel, for a long time interferes with the return of peristalsis. In the causation of the ileus of appendicitis, however, this is probably less potent than the two preceding factors.

The indications, therefore, are to evacuate the irritating contents of the peritoneal cavity and to reduce the handling of the gut to a minimum, especially if the peritoneum is involved to any extent. Thus in cases of abscess, the appendix, unless easily accessible, should not be removed, but operation at a later date should be advised, because the symptoms recur in many cases and sinuses are apt to develop.

The appendix was removed in 75 cases and the mortality was 11 per cent. The appendix was left intact in 106 cases and the mortality was 9 per cent., *i.e.*, the more limited operation secures a slightly lower mortality, but 8 per cent. of the cases had small sinuses on discharge, whilst only 4 per cent. occurred amongst those from whom the appendix was removed. Also 8 per cent. were readmitted—3 patients for sinuses developing after discharge; 1 for fæcal fistula; 4 for recurrent catarrhal appendicitis; 1 for a second appendicular abscess.

In spreading peritonitis cases, however, the source of infection should be removed at all costs, and the subsequent ileus guarded against by avoiding all the refinements of technique which have been devised for dealing with the stump of the appendix.

It is a very common custom to give repeated doses of purgatives as a routine measure after these operations in the hope of avoiding obstruction. A slight consideration of the pathology reveals at once the futility of this procedure. Perhaps the commencement of the jejunum may still possess a little tone and the purgatives may succeed in stimulating peristalsis, but if the poisonous nature of the pus and the inhibitory influence of the splanchnic nerves have produced any dangerous degree of relaxation further down the bowel, the purgative will merely irritate an organ which cannot react and do more harm than good. Obstruction will be precipitated, and the propulsion of the contents of the healthy upper gut into the lax toneless tube of the ileum will hasten the onset of distension and vomiting.

Thus in grave cases, ileus will be brought on earlier if purgatives are administered, and when the condition is not so precarious the bowels will act normally a few days later without any medical assistance.

A clear demonstration of the truth of these principles is afforded by the results of the injection of magnesium sulphate into the cæcum at the time of operation. Eleven cases have been recorded and in two ileus developed, which is an excessive

proportion, being 20 per cent., as contrasted with the 5 per cent. for abscesses and spreading peritonitis as a whole. This device is also very apt to give rise to a persistent faecal fistula; three of the cases suffered from this complication, *i.e.*, 27 per cent., compared with 4 per cent. obtained for all abscess and peritonitis cases. (This latter disaster is probably correlated with the fact that faecal fistulae are usually only troublesome when they arise from the involvement of the caecum in the necrotic process.)

The chief line of treatment, then, for ileus should be prophylactic, and consist in the avoidance of purgatives and food by the mouth. When the condition has once developed atropine may be of use to combat any reflex inhibition, but the prognosis is always very grave.

Enterostomy and irrigation of the bowel have been employed in some cases with subsequent closure of the wound and anastomosis of the gut after recovery from the acute symptoms. So far, however, the results have not been encouraging. Fifteen cases of ileus are recorded (*i.e.*, in 4 per cent. of operation cases) and the mortality is 73 per cent. In 4 of these enterostomy was performed and the mortality was 75 per cent.

The numbers are, of course, too small to be of much value, but they seem to indicate that death is not primarily due to obstruction, but to simultaneous lesions such as gangrene of the caecum, extreme septic absorption, and acute ulcers of the bowel. The last-named complication is not uncommon. One patient died from a perforating duodenal ulcer; 2 cases have occurred of acute ulceration of the ileum; and 5 of the caecum; whilst in 2 other cases acute ulceration occurred at some unspecified point in the large or small gut.

The last condition to consider is—

(5) Acute intestinal obstruction induced by bands and adhesions. It is delayed operation which is most often responsible for these cases.

General matting, as in tuberculous peritonitis, where the coils are glued together in normal relationships, does not often

produce obstruction. A more dangerous type of adhesion is a strong band passing from the cæcum to the small intestine, its attachment to the cæcum corresponding more with the point to which the drainage-tube extended than with the site of the appendix stump. Consequently the rule should be to pass the drain, wherever possible, to the outer side of the large gut and avoid proximity with the small intestine. In other cases the gut, working its way between the long pelvic drainage-tube and the anterior abdominal wall, has adhered to the latter and eventually rotated and become strangulated. In other cases, again, a catarrhal appendicitis may have caused the tip of the appendix to become firmly attached to the omentum, and thus produced a bridge constricting the termination of the ileum. But in all cases the primary cause is delayed operation.

Even when a well-defined abscess has developed much can be done to minimise the risk of intestinal obstruction by paying attention to the method of drainage. It has been pointed out that not only is efficient drainage of the peritoneal cavity impossible, but that it is not always necessary. Many operations have now been performed at this hospital on cases of suppurative peritonitis, with entire omission of drainage; and so far as the mortality attending this course of action is concerned the results are hopeful.

Twelve cases are recorded, and of these 8 made uninterrupted recoveries, although in three of them there was considerable supuration in the wound. Residual abscesses were opened in 3 cases. Death from gangrene of the abdominal wall occurred in 1 case; *i.e.*, the mortality is 8 per cent. as opposed to the mean, 20 per cent. But the cases include an undue proportion of early operations, and this may account for much of the diminution in the death rate.

An analysis of the conditions found is as follows:—

Localised abscesses	4
Spreading peritonitis	7
Acute perforation	1

It is evident that free drainage is not in all cases so essential as it was at one time thought to be. But to avoid local suppuration in the parietes, and the excessive proportion of ventral herniæ—17 per cent. as opposed to the average 2 per cent.—some slight drainage is desirable. Perhaps the best method is to place a short tube containing gauze just through the abdominal wall so as to reach the peritoneal cavity, and to remove it in about three days. In women this may be supplemented by drainage per vaginam, which has yielded uniformly excellent results in the few cases in which it has been adopted. At the operation itself great care should be taken to pack off the margins of the wound and to minimise contamination of the muscle and connective tissue layers with pus which, in early cases, contains pyogenic organisms of great virulence.

C. Let us now pass on to the third question. Operation is not always feasible. It may be contra-indicated by the presence of other lesions, and in many cases, the assistance of a skilled abdominal surgeon will not be immediately available. Furthermore, there is the period of anxious waiting during the first twenty-four hours to consider. What should the treatment be under these circumstances?

Several years ago A. J. Ochsner introduced a method of treatment entirely unlike that previously in vogue. It is the most logical system which has yet been put forward and the one which accords best with the pathology of the disease. Its author claims to have obtained wonderful results with it, and the arguments on which it is based are very convincing.

He maintains that the two essential factors are:—

- (1) Complete rest.
- (2) The prevention of the spread of peritonitis.

(1) *Rest*.—Many physicians have urged that repeated small doses of purgatives have a beneficial action by reason of the gentle massage produced by the peristalsis set up. This appears plausible enough, but is in reality absurd. Every modern surgeon would condemn massage and movement for a septic joint: in fact, the most recent treatment is diametrically

opposite, and with a view to the production of anti-bodies, local stagnation is often induced by Bier's methods.

That rest is the essential treatment for septic lesions is indeed a surgical commonplace of old repute, and Nature's reaction seems to be expressly designed to attain this end in appendicitis. Pain and tenderness minimise voluntary movements, rigidity protects the part from outside disturbance, whilst the inhibition of peristalsis insures a freedom from local agitation. These efforts should be seconded by our therapeutic measures, and food, purgatives and cold applications studiously avoided.

(2) *Prevention of the Spread of Peritonitis.*—A very large proportion of deaths can be attributed directly or indirectly to the extension of the peritoneal infection, and this should be guarded against carefully.

The immediate surroundings of the appendix are the cæcum, the parietal peritoneum over the ilio-psoas, the termination of the ileum, and the coils of small intestine. Clearly the least efficient part of this barricade is towards the middle line where the mobility of the small intestine is a constant source of danger. Pain minimises the movements of the ilio-psoas. The cæcum is emptied and then remains at rest. Movements of the bowel are inhibited, and the great omentum endeavours to aid in the attempt to shut off the process from the general peritoneal cavity. The whole reaction is co-ordinated to secure one end, the prevention of spread of the infective process by mechanical agencies. Yet it is a very common practice to attack the one weak spot in the protective armour of the appendix, and stimulate intestinal movements by the administration of purgatives.

The treatment as advocated by Ochsner is—

(1) Give no food and no purgatives by the mouth. In reference to this point he justly observes that no case of death from appendicitis has been recorded in which this principle was adhered to from the commencement of the attack. He further points out, if food is withheld what need is there for purgatives?

(2) Relieve thirst by rinsing the mouth with cold water and administering small and frequent warm rectal salines. These salines should be as warm as possible to avoid stimulation of peristalsis. Cold enemata, like cold packs, increase intestinal movements and may even produce colic.

(3) Relieve nausea and vomiting by gastric lavage, repeated if necessary.

(4) Supply some nutriment in the form of small enemata.

(5) Relieve pain by hot fomentations.

(6) Keep the patient at rest in the "Fowler" position.

These rules may at first seem somewhat empirical, but they can be shown to rest on a scientific basis, and to agree closely with the dictates of pathology. The clinical picture presented by any disease is broadly made up of two components:—

(a) The *Lesion* or destructive effects of the pathological stimulus;

(b) The *Reaction* of the organism to the adverse conditions.

In the earliest stages of the attack the predominating element is usually the reaction, the symptoms of which may at this time be most easily separated from those of the lesion, and give indications for a rational line of treatment.

The first and most constant manifestations of appendicitis are:—

(1) Constipation.

(2) Vomiting and severe distaste for food.

(3) Rigidity over the appendix.

(4) Those common to all septic infections.

An inquiry into the pathology of each of these will suggest a system of treatment in accord with scientific principles.

(1) *Constipation*.—The splanchnic nerves exercise an inhibitory influence on the muscle of the intestinal wall, and whenever strongly stimulated, *e.g.*, in biliary or renal colic or in affections of the ovary, peristalsis is delayed and constipation results, combined in many instances even with distension. Appendicular pain acts in a very similar manner, but here the issue is complicated by the proximity of the ileo-cæcal valve, a mechanism

exhibiting distinct physiological specialisation. The same splanchnic nerves, which inhibit the greater part of the gut, act as motor nerves to the ileo-cæcal sphincter, and local peritoneal stimulation produces a local splanchnic reflex, *e.g.*, perforation of an appendix or exposure of the region to cold will bring about closure of the ileo-cæcal valve and inhibition of the ileum, whilst the muscular tone of the duodenum and stomach may remain normal. It follows from these considerations that inflammation in the appendix will produce intestinal obstruction in the small intestine. This conclusion is supported by the frequent occurrence of indicanuria, and, as Dr. Hertz has pointed out, by the absence of cæcal sounds after perforation. Also, it is a matter of almost universal surgical experience that at operations for appendicitis the cæcum is empty.

If this be the true pathology of the constipation it will explain why appendicitis sometimes simulates intestinal obstruction, and why the onset of pain often closely follows a meal; also why purgatives often apparently relieve the patient, for the pain and discomfort are largely the result of stretching of the inflamed peritoneum by the distended bowel, and this distension being overcome, the attack proceeds as freely as before, but may be sufficiently mild in type to come to an end, notwithstanding the disturbing influence of the purgatives; purgatives abolish the pain, but the disease is cured not by them, but in spite of them. If, however, the lesion is one of any gravity it is hurried along its course towards perforation and similar catastrophes. The treatment suggested is the withholding of all purgatives at the commencement of an attack.

In a few cases, it is true, diarrhœa marks the onset of the disease, but this is usually due to a pelvic position of the appendix which, irritating the peritoneum around the rectum and sigmoid, stimulates the colon to excessive action.

(2) *Vomiting*.—This is distinct from the stercoraceous vomiting occurring later, after the development of spreading peritonitis, and is not persistent as a rule, but may be so if a meal has been taken recently. It is a reflex condition accompanying the intes-

tinal obstruction produced in the manner already described. Teleologically it is an attempt to prevent any more food from passing through the ileo-cæcal region. Intimately related to it is the severe distaste for food, and they indicate clearly that nothing should be allowed to gain access to the intestinal tract by way of the mouth; all food should be withheld.

Naturally one would like to treat so distressing a symptom, but vomiting is Nature's remedy, and the rational method is rather to assist the process of ejection of the pre-cæcal food by washing out the stomach. Of course, purgatives, by relieving the obstruction, will usually curtail the vomiting, but treatment which allays the symptoms and intensifies the lesion must of necessity be pernicious.

(3) *Rigidity*.—This local increase of muscular tone acts as a splint for the protection of the appendix. Attention is called to this function by the tenderness and pain. Its indications are almost universally followed, and the patient kept at rest in bed.

(4) *Symptoms common to other Septic Lesions*.—The significance of these is widely recognised. Protection is afforded against loss of heat whilst antipyretics are avoided and local hyperæmia increased by the application of hot fomentations. Some physicians have recommended that the pain should not be treated by heat, but by ice packs; this is obviously bad practice, for whilst heat acts as an intestinal sedative, cold increases peristalsis, which is the one thing to be avoided.

It can be seen at a glance that this treatment, evolved from physiological inquiry, agrees very closely with that deduced by Ochsner from his two postulates, viz., Rest and Prevention of the mechanical spread of peritoneal infection. Moreover, Ochsner claims that it has stood the test of practical experience, and maintains that, if the opportunity of operating during the first thirty-six hours has gone by, this treatment, persisted in, will tide the patient over the dangerous period. By this means a case which presents the characters of an acute perforation will eventually be operated on in the quiescent period, and appendicular abscesses requiring immediate operation will be almost

unknown. It is no uncommon occurrence at operations in the quiescent period to find a perforation safely shut in by matted adhesions, or the appendix a short stump, the result of the sloughing of the distal part during some previous attack, whilst in 5 per cent. of the interval operations proof is found of an old abscess, either as inspissated pus or a small thick-walled cavity. Furthermore, the evidence of the medical wards discloses the fact that 5 per cent. of the abscesses discharge spontaneously into the gut or per vaginam.

Ochsner's statistics show splendid results, but in the hands of other workers his methods have not proved so satisfactory. One interesting point recently brought out is that under this treatment the leucocytosis steadily falls, whilst the single administration of a purgative causes it to rise again rapidly.

It seems to be the most logical expectant treatment where immediate operation is impossible, but whether by its means all operations on the appendix will at last become interval operations is more than doubtful.

In the present paper an attempt has been made to demonstrate the following points:—

(1) The advisability of operation within the first thirty-six hours in all cases of appendicitis with a definite onset of severe symptoms not subsiding in twenty-four hours.

(2) That the tendency for peritoneal infection to remain localised increases with the age of the patient.

(3) That purgatives are contra-indicated—

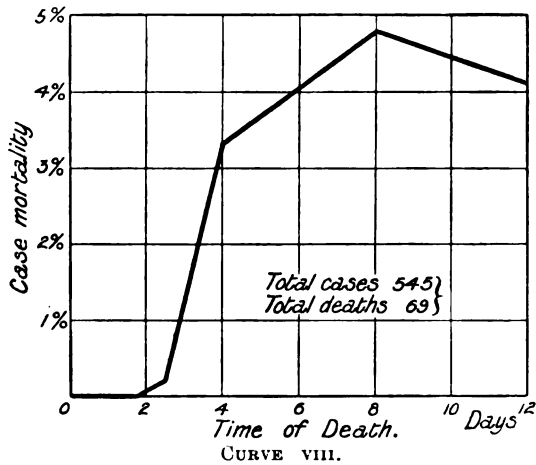
(a) As treatment for definite attacks of appendicitis.

(b) As a means of preventing post-operative ileus.

(4) That peritoneal drainage should be reduced to a minimum.

(5) That Ochsner's methods afford the most rational expectant treatment.



CASE MORTALITY AT VARIOUS INTERVALS FROM COMMENCEMENT OF
ATTACK.

In conclusion, I wish to thank the members of the Guy's Hospital Staff for permission to publish the results of cases under their care, and especially Mr. Rowlands and Dr. Rippmann, who have given me much help and many valuable suggestions.

ANALYSES.

II.—OPERATIONS IN FIRST THIRTY-SIX HOURS.

No. of Cases :—

0-24 hours	...	13	16.
24-36 hours	...	3	

Nature of Cases :—

Catarrhal inflammation	2
Empyema	4
Gangrene	2
Small local abscess	2
Peritonitis spreading from gangrenous appendix	2
Acute perforation	4

Interval from operation to discharge :—

Average	...	4 weeks.
Minimum	...	2½ weeks (catarrhal).
Maximum	...	6 weeks (spreading peritonitis).

Complications :—

Bronchitis	1
Fæcal fistula (closing spontaneously in 4 days)	1

*Deaths :—*Nil.

*Readmissions :—*Nil.

III.—INJECTION OF MAG. SULPH. INTO CÆCUM.

No. of Cases :—

Abscess 1 }
Spreading peritonitis 10 } 11.

Deaths :—

(Spreading peritonitis only), 3, *i.e.*, 30 per cent. (Average for spreading peritonitis, 42 per cent.)

Complications :—

Ileus, 2, *i.e.*, 19 per cent. (Average 1. Abscess 2 per cent. } 5 per
" 2. Spr. peri. 10 per cent. } cent.)

Intestinal obstruction by bands, 1.

Persistent faecal fistula requiring operation, 3, *i.e.*, 27 per cent.
(Average for abscess and spreading peritonitis, 4 per cent.).

IV.—RESULTS OF NON-REMOVAL OF APPENDIX IN ABSCESS CASES.

Appendix Removed.	Appendix Left in.
Mortality :—11 per cent.	9 per cent.
No. of Cases :—73.	106
On Discharge :—Small sinus in 4 per cent.	Small sinus in 8 per cent. Fæcal fistula 1 per cent.

Re-admissions in cases of non-removal :—

Sinus developing after discharge ... 3 }
Fæcal fistula 1 }
Catarrhal appendicitis 4 } 9, *i.e.*, 8 per cent.
Appendicular abscess 1 }

V.—RESULTS OF OMISSION OF DRAINAGE IN APPENDICITIS WITH PERITONEAL INFECTION.

No. of Cases :—12.

Deaths :—1, *i.e.*, mortality, 8 per cent. (note excessive proportion of early operations). (Cause of death—Gangrene of abdominal wall.)

Uninterrupted recoveries :—8. (Considerable suppuration in wound in 3 cases).

Residual abscess :—3.

Complications :—Lobar pneumonia and empyema, 1.

Condition at operation :—

Abscess (localised) 4 (one operation in first twenty-four hours).

Spreading peritonitis, 7 (one operation in first twenty-four hours).

Acute perforation, 1.

Readmissions for hernia :— 2, *i.e.*, 17 per cent. }

Average for cases operated on in 1906, 2 per cent. }

VI.—INTERVAL OPERATIONS.

A.—After expectant treatment at Guy's Hospital.

After attack 1.		Attack 2.		Attack 3.		Attack 4, etc.		After Abscess.			
♂	♀	♂	♀	♂	♀	♂	♀	♂		♀	
								No. Op.	Ab. Opened.	No. Op.	Ab. Opened.
12	11	4	3	4	5	0	2	1	1	2	1
23		7		9		2		5			

Total 46—(Catarrhal 41, Abscess 5).

B.—*Total operations:—*

No. of cases	250	
Deaths	3	Mortality 1·2 per cent.
Subsequent operation for hernia	2	Incidence 0·8 per cent.
Undiagnosed abscess	2	" 0·8 per cent.
Inspissated pus and old abscess cavity	12	" 5·0 per cent.

Causes of death:—

1. General peritonitis.
2. General pyæmia and septicæmia (small local abscess at appendix stump, and embolic foci in kidney).
3. Shock? Nothing found at post-mortem. (Matted adhesions broken down at operation.)

VII.—*READMISSIONS FOR VENTRAL HERNIA.*

Total readmissions, 1906–1909:—9.

Readmissions after operations performed, 1906:—2.

(No readmissions occurred after December, 1908.)

I.e. incidence after operations on acute appendicitis in 1906=2 per cent.

Hernia, subsequent to:—

1. Interval operations	2
2. Recurrent appendicitis	1
3. Diffuse peritonitis sewn up without drainage	2
4. Drainage of abscess	2
5. Plugging of wound to induce formation of adhesions some time before removal of appendix	1

Effect of belts:—

1. Developing after wearing a bandage	1
2. " " belt	1

(This hernia commenced during pregnancy.)

VIII.—*COMPLICATIONS.*

Complication.		Case Percentage.	Operation Per Cent.
PNEUMONIA	...	8	1·5
PLEURISY (without PN.)	...	16	2·9
R.	...	11	2·0
L.	...	3	0·5
+ Subphrenic abscess	...	4	0·7
EMPHYEMA	...	6	1·1
BRONCHO-PNEUMONIA	...	2	0·4
Simple	...	1	0·2
+ Gangrene	...	1	0·2
BRONCHITIS	...	2	0·4
PORTAL PYÆMIA	...	6	1·1
ILEUS (paralytic)	...	15	2·7
INTESTINAL OBSTRUCTION (bands, etc.)	...	6	1·1
FÆCAL FISTULA	...	23	4·1
Transient...	...	13	2·3
Persistent	...	8	1·5
URINARY FISTULA	...	1	0·2
PYURIA	...	2	0·4
ULCERATION OF GUT	...	10	1·8
Duodenum	...	1	0·2
Ileum	...	2	0·4
Cæcum	...	5	0·9
? Ileum ? Colon	...	2	0·4
SUBPHRENIC ABSCESS	...	6	1·1
GANGRENE OF ABDOMINAL WALL	...	1	0·2
GENERAL PYÆMIA AND SEPTICÆMIA	...	3	0·6
SALPINGITIS	...	2	0·4
PERICARDITIS	...	2	0·4
ACUTE HYDROCELE	...	1	0·2

TABLES A—Q.
1906—1909 (Inclusive).

1. No Cases are included in which the diagnosis was doubtful.
2. "ACUTE" Appendicitis refers to cases requiring operation during an attack.
3. "CATARRHAL" Appendicitis refers to cases recovering under expectant treatment.
4. "RECURRENT" Appendicitis refers to cases in which there was a history of repeated slight attacks of pain extending over a considerable period of time.
5. "ABSCESS" implies a localized collection of pus.
6. "SPREADING PERITONITIS" includes:—
 - a. Ruptured abscesses.
 - b. Insidious spread from a gangrenous appendix or from a partially localized abscess.
 - c. Acute perforations in which operation was too late to prevent a spreading infection.
7. "OTHER" Cases include:—
 - a. Severely congested appendices.
 - b. Appendices intact but distended with pus. in which early operation avoided the development of either a localized abscess or spreading peritonitis.
 - c. Gangrenous appendices
 - d. Acute perforations ...

A.—CASE MORTALITY AND AGE. (Mean = 12.7 per cent.)

♂ Age.	Deaths.	Cases.	Mort. Per cent.	Mort. ♂ + ♀ Per cent.	♀ Age.	Deaths.	Cases.	Mort. Per cent.
1-5	1	12	15	19	1-5	2	3	28
6-10	8	48			6-10	6	25	
11-15	7	63	12	11	11-15	2	34	11
16-20	9	64			16-20	7	50	
21-25	4	53	9	7	21-25	3	57	5
26-30	5	44			26-30	2	39	
31-35	2	22	9	6	31-35	1	25	4
36-55	6	48	12.5	9	36-55	1	31	3
56-75	6	15	40	30	56-75	0	5	—

B.—MORTALITY AND ATTACK.				C.—MORTALITY AND STAGE OF ATTACK.			
Attack.	Cases.		Mort.	Operations.		Deaths.	Mort.
	Cases.	Deaths.		Ops.	Deaths.		
1	392	48	Per cent. 12.2	237	47	0	0
2	69	5	7.2	39	5	0	0
3	26	1	3.8	13	1	1	0.2
4 and more	24	2	8.3	18	2	18	3.3
Total	545	63	12.7	340	64	25	4.8
	Interval operations.			250	3	24	4.1

D.—OPERATION MORTALITY AT VARIOUS STAGES OF ATTACK.												E.			
Time of Operation.	Abscess.			Spreading Peritonitis.			Other Cases.			Total.		Appendix Removed.		Appendix Left In.	
	Op.		M'y	Op.		M'y	Op.		M'y	Op.		Op.		Op.	
	D's	P.c.		D's	P.c.		D's	P.c.		D's	P.c.	D's	P.c.	D's	P.c.
0-24 hrs.	1	0	0	4	0	0	8	0	0	13	0	73	8	106	9
24-36 "	1	0	0	1	0	0	1	0	0	3	0				
36-48 "	10	0	0	23	5	22	6	0	0	39	5	84	27	17	77
48-72 "	12	2	17	11	6	55	7	0	0	30	8				
3-5 days	33	5	15	39	16	41	7	0	0	79	21				
6-10 "	63	4	6	24	15	62	8	0	0	95	19	207	35	193	21
Later	60	7	12	7	4	57	14	0	0	81	11				
Total	180	18	10	109	46	42	51	0	0	340	64				

D.—OPERATION MORTALITY AT VARIOUS STAGES OF ATTACK.

E.

F.—COMPLICATION INCIDENCE AFTER OPERATION AT VARIOUS STAGES OF DISEASE.

Complication.	1st 36 hours.			36-72 hours.			3-5 days.			6-10 days.			Later.			Total.			
	Comp.	Ops.	P cent.	Comp.	Ops.	P cent.	Comp.	Ops.	P cent.	Comp.	Ops.	P cent.	Comp.	Ops.	P cent.	Comp.	Ops.	P cent.	
Melus	0	16	0	2	69	2.9		7	79	8.8	5	95	5.2	1	81	1.2	16	341	4.4
Pulmonary .. .	1	16	6.2	6	69	8.7		12	79	15.2	7	95	7.3	2	81	2.4	30	341	8.8
Portal pyæmia ..	0	16	0	0	69	0		2	79	2.5	2	95	2.2	2	81	2.4	6	341	1.7
Fæcal fistula. . .	1	16	6.2	2	69	2.9		3	79	3.8	9	95	9.5	8	81	9.8	24	341	7.0
Subphrenic abscess	0	16	0	0	69	0		4	79	5.1	2	95	2.2	0	81	0	6	341	1.7
Total (all complications)	2	16	12.5	14	69	20.3		19	79	24.1	25	95	26.3	14	81	17.3	74	341	21.7

(Cases with more than one complication treated as units.)

G.—COMPLICATION MORTALITY AFTER OPERATION IN VARIOUS STAGES OF DISEASE.

Complication.		Comp.	D'ths	Mort.	Comp.	D'ths	Mort.	Comp.	D'ths	Mort.	Comp.	D'ths	Mort.	Comp.	D'ths	Mort.
Ileus												15	11	78
Pulmonary												30	17	57
Portal pyæmia												6	6	100
Fæcal fistula												24	4	17
Subphrenic abscess												6	5	83
Total	2	0	0	14	6	43	21	11	52	27	12	44	35	47

H.—COMPLICATION INCIDENCE FOR VARIOUS TYPES OF ATTACK. I.—COMPLICATION MORTALITY FOR VARIOUS TYPES OF ATTACK.

Complication	Abscess.			Spreading Peritonitis.			Other Cases.			Abscess.			Spreading Peritonitis.			Other Cases.		
	No. of Comp. Cases.	No. of Comp. Cases.	Pcent.	Comp.	Cases.	Pcent.	Comp.	Cases.	Pcent.	No. of Comp.	No. of Comp.	D'ths.	Mort.	Pcent.	Comp.	D'ths.	Mort.	Pcent.
Ileus	4	180	2·2	11	109	10	0	51	0	4	3	75	11	8	73	0	0	—
Pulmonary	12	180	6·6	17	109	15·6	1	51	2	12	5	42	17	13	76	1	0	0
Portal pyæmia	2	180	1·1	4	109	3·7	0	51	0	2	2	100	4	4	100	0	0	—
Fæcal fistula	14	180	7·7	6	109	5·5	2	51	4	14	1	7	6	3	50	2	0	0
Subphrenic abscess	1	180	·6	5	109	4·6	0	51	0	1	1	100	5	4	80	0	0	—
Total	34	180	19	30	109	27·5	6	51	12	34	11	32	30	21	70	5	0	0

J.—INCIDENCE OF COMPLICATIONS IN VARIOUS ATTACKS.

Complication	Attack 1.			Attack 2.			Attack 3.			Recurrent			Total.		
	Comp.	Cases.	Per Cent.	Comp.	Cases.	Per Cent.	Comp.	Cases.	Per Cent.	Comp.	Cases.	Per Cent.	Comp.	Cases.	Per Cent.
Ileus	12	392	3.0										15	549	2.7
Pulmonary	23	392	5.6										29	549	5.3
Portal Pyæmia	6	392	1.5										6	549	1.1
Fæcal Fistula	18	392	4.5										25	549	4.6
Subphrenic Abscess	5	392	1.3										6	549	1.1
Total (all complications) ...	56	392	14.3										75	549	13.8

(Cases with several complications considered as units.)

K.—COMPLICATION MORTALITY.

Complication.	1.			2.			3.			Recurrent.			Total.		
	No. of Comp.	Deaths.	Mort. Pr. Cnt.	Comp.	Deaths.	Mort. Pr. Cnt.	Comp.	Deaths.	Mort. Pr. Cnt.	Comp.	Deaths.	Mort. Pr. Cnt.	Comp.	Deaths.	Mort. Pr. Cnt.
Ileus	12	8	66.6										15	11	73
Pulmonary	22	13	59.1										29	17	59
Portal Pyæmia	6	6	100										6	6	100
Fæcal Fistula	18	3	16.6										25	4	16
Subphrenic Abscess	5	4	80										6	5	83
Total	56	27	48.2	9	5	55	2	1	50	1	0	—	75	39	48

L.—AGE INCIDENCE OF ATTACKS NECESSITATING OPERATION.

Age, ♂	A.		F.		A.		F.		Total.		Total.	Acute, Following Recurrent.		Total.	
	Abscess. Attack 1.	Spreading Peritonitis. Attack 1.	Attacks, 2, 3, etc.	Attacks, 2, 3, etc.	Attacks, 2, 3, etc.	Attacks, 2, 3, etc.	Attacks, 2, 3, etc.	Attacks, 2, 3, etc.	Cases.	Per cent. at given age.		Cases.	Per cent. at given age.	Cases.	Per cent. at given age.
1-5	4	4							8	4.5				8	3.8
6-10	15	12							29	16.5				31	14.6
11-15	23	15							39	22.1				43	20.3
16-20	15	8							29	16.5				39	18.4
21-25	15	9							24	13.6				27	12.7
26-30	9	5							14	8.0				20	9.4
31-35	7	2							9	5.1				11	5.2
36-55	11	4							16	9.1				22	10.4
56-75	7	1							8	4.5				11	5.2
Total ...	116	60			15	6			176	100	5	15	5	212	100

♀															
1-5	0	0							1	1.3				3	9.6
6-10	6	6							12	15.8				14	12.2
11-15	7	4							12	15.8				20	17.4
16-20	11	4							15	20.0				22	19.1
21-25	8	5							14	18.4				26	22.6
26-30	3	2							6	7.9				9	7.8
31-35	2	1							3	4.10				5	4.3
36-55	7	3							10	13.0				13	11.3
56-75	3	0							3	4.0				3	2.6
Total ...	47	25			19	9			76	100	5	16	10	115	100
♀ + ♂ ...	163	85			34	15			252	—	10	31	15	327	—

M.—CASES RECOVERING UNDER EXPECTANT TREATMENT.							N.—AGE INCIDENCE OF CASES OF ALL TYPES.			
Age. ♂	Catarrhal Attack 1.		Catarrhal Attack 2.	Catarrhal Attack 3.	Catarrhal Recurrent.	Total Catarrhal Attacks 1, 2, 3.	All cases with recurrent History (Age at 1st attack).		All cases, and interval operation cases. (Age at 1st attack).	
	Cases.	Per cent. at given age.					Cases.	Per cent.	Cases.	Per cent.
1-5	4	5.0				4	1	2.3	16	4.0
6-10	13	16.3				14	3	6.8	53	12.8
11-15	13	16.3				15	2	4.6	64	15.5
16-20	15	18.8				20	10	22.7	77	18.5
21-25	11	13.8				17	8	18.2	67	16.3
26-30	8	10.0				14	9	20.4	51	12.3
31-35	3	3.3				4	1	2.3	24	5.8
36-55	11	13.8				15	9	20.4	50	12.0
56-75	2	2.5				2	1	2.3	12	2.9
Total ...	80	100	18	5	6	105	44	100	414	100
♀										
1-5	0	0.0				0	1	1.9	3	1.0
6-10	8	13.3				9	1	1.9	23	7.6
11-15	8	13.3				12	6	11.3	43	14.0
16-20	17	28.3				20	4	7.5	64	21.0
21-25	9	15.0				21	17	32.0	74	24.6
26-30	7	10.2				12	9	17.0	42	13.8
31-35	5	8.3				8	8	15.0	28	9.0
36-55	5	8.3				7	7	13.0	24	8.0
56-75	1	1.7				2	0	0.0	4	1.0
Total ...	60	100	19	11	8	91	53	100	305	100
♀ + ♂	140		37	16	14	196	97		719	

Age. ♂	O.			P.			Q.				
	Per cent. of Peritonitis remaining localized, i.e., 100A/(A + F).			Per cent. of Cases requiring Operation, i.e., $\frac{100 \text{ Acute}}{(\text{Acute} + \text{Catarrhal})}$.			Ratio—Males/Females, i.e., $\frac{\delta}{\eta}$				
	Attack 1.	Attack 2, 3, etc.	Attack 1. ♂ & ♀	Attack 1.	Attack 2.	Attack 3.	With Recur- rent History.	Attack 1. ♂ & ♀	Acute. (Attack 1.)	Catarrhal. (Attack 1.)	Recurrent. (Ag-at-onset)
	Per cent.		Per cent.					Per cent.			
1-5	50		50					69	2.7	6.0	2.0
6-10	55		54					63	2.2	2.0	
11-15	60		61					65	2.1	1.2	1.4
16-20	69		68					50	1.8	1.0	
21-25	62		62					54	1.1	1.0	0.7
26-30	64		63					89	2.2	0.6	
31-35	77		75					50	1.2	1.0	
36-55	80		80					55	1.7	1.8	.7
56-75								65	3.6		
Total ...	66	71	66	63	23	17	10	56	1.8	1.1	0.8
♀											
1-5	0										
6-10	50										
11-15	64										
16-20	73										
21-25	61										
26-30	60										
31-35	66										
36-55	85										
56-75											
Total ...	65	68		44	30	15	16				

THE PHYSIOLOGY OF DIGESTION GASTRIC AND INTESTINAL.

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PART I.

INTRODUCTION.

Changes undergone by the Food-stuffs in the Alimentary Canal.—The use of the process of digestion is to alter the food-stuffs so as to fit them for absorption into the blood, by

means of which they may be carried to all parts of the body. In most cases the food-stuffs cannot be utilised in their original form by the living cells. It must be remembered that when we nourish ourselves at the expense of an animal or plant, we are taking in not only the current coin of the organism which is being used for the supply of energy to its vital processes, but also, and to a much larger extent, the framework forming the machinery of the organism, as well as its stores of carbohydrate or fat. The food-stuffs as we ingest them are in the most inactive form possible. Practically all of them are colloidal, free from taste or chemical reaction, and presenting no tendency to unite with oxygen, or indeed to undergo any change whatsoever, apart from the interference of living organisms such as bacteria. In a starving animal the stores of carbohydrate and fat and the protein structure of the inactive living cells have to be converted into a soluble form, transformed, so to speak, into currency, before they can be utilised by other living cells, such as those of the heart, for the discharge of their normal functions and the maintenance of the life of the animal. In the same way, when we take these colloidal or insoluble substances into our alimentary canal they have to be dissolved and rendered soluble or diffusible, in order to allow of their easy transference across the wall of the gut into the blood and their transport to the tissue cells. On fats and carbohydrates, therefore, the effect of digestion will be to render them soluble and diffusible, and to reduce them to a condition in which they can be directly assimilated by the cells of the body. These latter cannot deal, for example, with all kinds of carbohydrate. Many an animal cell will starve when presented with starch, dextrin, or any of the disaccharides, such as maltose, lactose, or cane sugar. It is necessary, therefore, that all the carbohydrates shall be reduced in the alimentary canal or in its walls to the form of monosaccharides. As regards proteins, the processes of digestion have a different significance according as we are dealing with their value as givers of energy or their value as builders up of the living protoplasm. If the proteins of the food are to

be oxidised and utilised as a source of energy, it is only necessary to render them soluble so as to assist their absorption. If, however, they are to be built up as integral parts of the living cells, to take the place of molecules which have been destroyed in the wear and tear of the processes of life, a much more profound change is necessary. The proteins of the cells from different parts of the body have different molecular constitutions. Not only do they differ among themselves, but they differ very largely from many of the proteins which may be taken in with the food. A child is able to obtain material for the growth of his brain cells, his muscle cells, or his liver cells, from a diet containing protein in the form of caseinogen, or of vegetable gluten, or of meat fibrin. A reference to the following tables will show the striking difference in composition between the various proteins of the food and the proteins which have to be formed from them in the living tissue.

We may take for example the manner in which the nitrogen is combined in the different proteins. For purposes of classification the nitrogen can be divided into three fractions, namely—

- (a) The portion which is driven off as ammonia by heating with alkalies or magnesia, the so-called ammonia or amide-nitrogen;
- (b) That contained in the form of monoamino-acids;
- (c) That contained as diamino-acids, or as bases such as guanidin, histidin, or arginin, etc., known as basic nitrogen.

In the following table is given the relative distribution of the nitrogen among these three groups in various proteins:—

Protein.	Amide-N.	Basic-N.	Monoamino-N.
Crystallised serum albumin ...	6.5	34.4	60.2
Crystallised egg albumin ...	8.5	21.3	67.8
Crystallised edestin ...	10.2	38.1	55.0
Caseinogen of milk ...	10.4	28.9	62.0
Serum globulin ...	8.9	25.0	68.3

Still greater differences are noticeable when we examine the content in certain individual constituents of the protein molecule, thus:—

Protein.	Arginin.	Lysin.	Histidin.	Tyrosin.	Cystin.
Edestin	14·07	—	—	—	—
Caseinogen	4·84	5·80	2·59	4·5	—
Blood fibrin	—	—	—	3·82	1·17
Gluten fibrin (wheat)	3·05	—	1·53	—	—
Zein (maize)	1·82	—	0·81	—	—
Egg albumin	—	—	—	1·5	0·29
Serum albumin	—	—	—	2·0	2·15

It is evident that to form serum albumen, for instance, out of wheat gluten, an entire reconstruction is necessary. This can only be accomplished by taking the protein molecule to bits, and by selecting certain of its constituent parts and building these up in the proper proportions to form a new protein molecule. For the purposes of nutrition, therefore, the changes in the protein molecule in the intestine must be profound, and the extent of the change must be greater the more variation there is in the composition of the protein of the food from the composition of the proteins of the tissues.

In primitive alimentary canals every cell lining the canal may be endowed with amœboid properties and be capable of devouring the food particles; the subsequent changes in the food particles to fit them for their journey through the rest of the body being performed in the body of the cell itself. In all the higher animals, including ourselves, the greater part of the preparation of the food is accomplished *extracellularly* in the lumen of the alimentary canal, and the changes are effected by means of special digestive juices which are formed by the activity of masses of cells, produced as outgrowths from the wall of the canal. The digestive juices attack the food-stuffs by means of ferments, and in every case the action of these ferments is hydrolytic, the food-stuffs taking up one or more molecules of water and undergoing dissociation into simpler molecules. Since each class of food-stuff requires a different ferment, a great variety of ferments are concerned in the pro-

cesses of digestion. As the end result of digestion, the enormous variety of food taken by man is reduced into a fairly small number of simpler bodies. These end products are:—

- (1) Carbohydrates. The monosaccharides: glucose, fructose or lævulose, and galactose.
- (2) Fats: fatty acids, or (in alkaline medium) soaps, and glycerin.
- (3) Proteins. Here we have a great variety of mono- and diamino-acids, which may be enumerated as follows:—

Monoamino-Acids:—

Glycine (aminoacetic acid)	Monobasic acids of fatty series.
Alanine (aminopropionic acid)	
Serine or oxyalanine (oxyaminopropionic acid)	
Aminovalerianic acid	
Leucine (aminoisobutylacetic acid)	
Isoleucine (aminocaproic acid)	Dibasic acids.
Aspartic acid	
Glutamic acid	
Phenylalanine	Benzene (aromatic) derivatives.
Tyrosine (oxyphenylalanine)..	
Proline (pyrrolidine carboxylic acid)	
Oxyproline (oxypyrrolidine carboxylic acid)	Heterocyclic compounds.
Tryptophane (indolaminopropionic acid)	

Diamino-Acids and their compounds:—

Lysine (diaminocaproic acid)	The "hexone bases."
Arginine (guanidinaminovalerianic acid)	
Histidine (a pyrimidine derivative)	
Diaminotrioxydodecaic acid	Derived from a 12 carbon acid.
Cystine (derived from aminothio-propionic acid)	Sulphur-containing body.

The whole of these digestive changes in the food-stuffs are to be ascribed to the action of ferments. Those constituents of the food which undergo no oxidation in the body, such as the water and salts, are practically unchanged in the alimentary canal, and are absorbed in their original form into the blood.

In the course of the following pages we shall have to deal in turn with the mechanisms of secretion of the digestive juices, the changes wrought by them on the food-stuffs, and the movements of the alimentary canal whereby all parts of the food are brought into intimate admixture with the juices, and are moved from one segment of the canal to the next in accordance with the needs of the organism. Finally, we shall have to consider the last act in the process of digestion, namely, the taking up of the dissolved food-stuffs by the mucous membrane lining the alimentary canal, so that they may be incorporated with the fluids and tissues of the body.

PART II.

THE ACTUAL COURSE OF DIGESTION.

It is only within the last few years that physiologists have been in a position to form a complete picture of the changes undergone by the food in its whole course through the alimentary canal. Previously we have had to piece together the processes from an imperfect study of the influence of extracts of mucous membrane on the food-stuffs, and from the observation of accidental cases of fistulæ opening into the various parts of the alimentary canal. Recent improvements in surgical technique have rendered it possible for physiologists to establish fistulæ at will in any part of the alimentary canal, and, while preserving the animal in a state of health, to draw off at any desired phase in the processes of digestion the products of digestion in any segment of the canal. The fistula method is really one of the oldest of those used in experimental physiology. Thus, in the collected works of De Graaf there is a plate of a dog provided with fistulæ of the salivary ducts and of the pancreatic duct. This method was elaborated by Thiry and Vella in the case of the intestine, and was employed by

Heidenhain for the study of the secretion of gastric juice. It first found wide application, however, in the hands of Pawlow and his pupils, who have shown that it is possible, by the use of the aseptic method, to make fistulæ in any part of the alimentary tract. In a series of papers recently published by London he describes the course of digestion of meals of various characters in dogs which had been provided with fistulæ in one of the following places:—(a) gastric fistula (into the fundus of the stomach); (b) pyloric fistula (on the duodenal side of the pylorus); (c) duodenal fistula (about one foot below the pylorus); (d) jejunal fistula (about the middle of the small intestine); (e) ileum fistula (just above the cæcum).

We may take as an example the course of digestion of a meal composed of 200 grammes of bread. This is eaten by the animal, mixed with saliva and swallowed. On arriving at the stomach it gives rise to the secretion of gastric juice. In a series of special experiments London showed that on the average 200 grammes of bread evoked the secretion of 20 gms. of saliva, about 10 gms. of mucus from the coats of the stomach, and about 315 gms. of gastric juice. The secretion of gastric juice is continuous during the whole time that the food remains in the stomach. In the animal with a pyloric fistula, one to two minutes after the meal had been taken, a few drops of alkaline fluid were extruded from the opening. From three to eight minutes after the conclusion of the meal repeated small quantities of clear acid gastric juice were extruded. The first admixture of the food with the outflow from the fistula occurred at eight to twelve minutes after the completion of the meal, and after this time the pylorus continued to open at regular intervals of ten to forty seconds, discharging each time a small amount of fluid composed of particles of undigested bread mixed with gastric juice. One and a half hours later the pylorus began to open less regularly, and the fluid became of a more pasty consistence, devoid of lumps of undigested bread. In the fourth, fifth and sixth hours after the meal the pylorus opened only once every one or two minutes, and towards the end of

this period the fluid extruded was clear. The following table shows the percentage amount of food taken which had left the stomach at the end of each hour after the meal:—

1st hour	32.6 per cent.
2nd	„	17.9 „
3rd	„	29.5 „
4th	„	1.87 „
5th	„	6.66 „
6th	„	4.21 „

The large proportion of the ingested food leaving the stomach during the first two or three hours can hardly be regarded as normal. As we shall see later, the passage of the acid chyme into the duodenum tends, by means of a local reflex, to inhibit the opening of the pylorus. Since in these experiments there was a free outflow from the pylorus and the food was not allowed to enter the duodenum, this reflex was absent. The gastric contents obtained in this way were analysed in order to find what changes had been wrought on the food by the gastric juice. It was found that 32 per cent. of the bread had been brought into solution. This solution had affected the proteins more than the carbohydrates. Thus, 67 per cent. of the nitrogen had been brought into soluble form, consisting chiefly of albumoses and peptones. No amino-acids were formed. Only 25 per cent. of the starch of the bread had been rendered soluble, and of this, 21 per cent. were in the form of dextrine and 4 per cent. in the form of sugar. No absorption, however, either of the digested proteins or of the digested carbohydrates was ever found to take place in the stomach.

Duodenal Digestion.—The influence exerted by the juices, pancreatic juice, bile and succus entericus, poured out on the food in the duodenum, was studied by analysis of the intestinal contents leaving the intestine by a fistula, either at the lower end of the duodenum, or in the jejunum, or in the ileum. From the duodenal fistula the expulsion of food occurs at repeated intervals, but in a somewhat irregular fashion, its movements being determined partly by the contractions of the stomach and

partly by those of the duodenal wall. Usually a large gush is followed by a series of small gushes. Although only a foot intervenes between the duodenal fistula and the pyloric fistula, a great difference is observed in the character of the intestinal contents obtained in the two cases. The outflow from the duodenum, being mixed with the pancreatic juice and the bile, is yellow in colour and increased in amount. With a meal of 200 gms there is secreted on the average 130 gms. bile and 140 gms. pancreatic juice. During its passage through the duodenum the carbohydrates of the food undergo considerable changes, so that even one foot below the pylorus we find that one-half to three-fifths of the carbohydrates have been converted into dextrine and sugar. A further digestion of the proteins also takes place amounting to about one-tenth of the whole protein taken with the food.

On deducting the amount of juices which have been added to the food it is found that even over this short length of intestine absorption has taken place of about one-sixth of the ingested food, about one-fourth of the carbohydrates having been absorbed and about one-eighth of the proteins.

When we examine a dog which has a fistula about the middle of its small intestine we find an outflow beginning six to fifteen minutes after the meal, and lasting six or seven hours. The outflow is by small gushes repeated at intervals of five to ten seconds separated by intervals of one to five minutes, during which nothing appears at the orifice of the cannula. The material obtained is quite different in character from that flowing from the duodenal fistula. The pasty character has disappeared, and the material now forms a frothy, orange-yellow, even jelly-like mass with practically no trace of undigested bread.

From a fistula in the ileum the outflow occurs at long intervals of three to fifteen minutes and is much scantier than that obtained from the jejunal fistula, and consists of a thick jelly-like, orange-coloured mass. Both proteins and carbohydrates are entirely digested, and in the case of the former the chief products of digestion consist of amino-acids. Thus,

in one experiment after four large meals of 500 gms. of meat each had been given, in order to obtain sufficient quantity for analysis, 175 gms. of soluble substances were obtained. From this were isolated tyrosin, leucine, alanine, aspartic acid, lysine, and traces of arginine and histidine.

When a fistula is made in the cæcum there is no outflow until four or five hours after the meal has been taken. The material from the gut is then extruded in faecal-like masses at long intervals of one-half to one hour. This regular outflow lasts for about six hours. The reaction of the contents is strongly alkaline, no food particles are left, and the material contains merely debris of cells, with small traces of sugar, dextrin and unaltered starch. The absorption of the food-stuffs is practically complete by the time that the food has reached the lower end of the small intestine.

The following table gives the total amounts obtained in a series of experiments from the different fistulæ after administration of 200 gms. of bread, and also the percentage amount of food-stuffs which had been absorbed before the food had arrived at the level of the fistula in question:—

	Total amounts obtained from 200 gms. bread.	Absorbed. per cent.
Pyloric fistula ...	691 gms. ...	0
Duodenal fistula ...	691 " ...	17·45
Jejunal fistula ...	585 " ..	37·77
Ileum fistula ...	412 " ..	67·65
Cæcal fistula ..	80 " ..	94·34

The whole process of digestion evidently involves a complicated chain of events in which each phase is dependent on the preceding phase, and serves to evoke the phase which will follow. The food taken into the stomach causes in some way or other the secretion of an amount of gastric juice proportionate to the amount and to the nature of the food taken. The movements of the stomach which serve to mix the food with the gastric juice, and to expel it into the duodenum, are evidently also adapted to the rate at which digestion takes place and the amount and strength of the gastric juice itself. They are also

dependent on events occurring lower down the alimentary canal, so as to prevent the food being passed into the intestine at a quick rate by this viscus. As soon as the food enters the duodenum, the pancreatic juice and bile are poured into the lumen of the gut just at the moment and in proportion as they are required. We shall see later on that these juices are not equally important for all three classes of food-stuffs, and we find that they are therefore not secreted in equal proportions for all food-stuffs, that carbohydrates, for instance, evoke the secretion of much pancreatic juice, but little bile, whereas the reverse is the case on ingestion of fats. As the food passes down the gut the movements of its muscular wall must be so graduated that the food, while being mixed with the digestive juices, is not hurried too rapidly through the intestine, so that by the time that it reaches the lower end of the small intestine, not only digestion, but absorption, are practically complete. In the following chapters I shall have occasion to analyse each of the phases of digestion and to unravel the complex chain of mechanisms which determine the adaptation of the digestive processes as a whole to the needs of the animal.

PART III.

DIGESTION IN THE STOMACH.

1. *The Secretion of Gastric Juice.*—Dr. Beaumont in his researches on the functions of the stomach, carried out on the famous case of Alexis St. Martin, observed that, when food was taken, little drops of fluid were rapidly poured out on the surface of the gastric mucous membrane. These drops of fluid consisted of gastric juice. Many devices have been employed to obtain gastric juice for analysis. Thus, sponges in perforated metal capsules were introduced into the stomach either by the œsophagus or through a gastric fistula. Other observers attempted to induce a flow of this juice by mechanical stimula-

tion of the mucous membrane through a fistula. Most of the work, however, on the influence of gastric juice has been obtained by using artificial juice made by extraction of the mucous membrane with glycerine or by dissolving the mucous membrane in weak hydrochloric acid. The first satisfactory methods of obtaining gastric juice free from admixture with food and for studying the conditions of its secretions were devised by Pawlow. Having established a gastric fistula in the ordinary way, Pawlow adopted the method of dividing the œsophagus in the neck and bringing the two ends to the surface. Animals operated on in this way can be fed by introduction of fluid food through the lower end of the œsophagus or by the introduction of fluid or solid material directly into the stomach. They can also eat a meal in the ordinary way, but the food which is swallowed will always fall out of the opening of the œsophageal fistula in the neck. In order to collect juice from such an animal it is starved for twenty-four hours, and then given a draught of 300 c.c. normal salt solution in order to wash out any debris from the last meal adhering to the walls of the stomach. Thirty minutes later it is given a meal of meat. This it eats with avidity, but since the food cannot reach the stomach, its hunger is not satisfied, and it will continue to eat the same meat over and over again for two or three hours. Five minutes after the beginning of this "sham feeding," as Pawlow calls it, gastric juice begins to drop from the fistulous opening, and in this way large quantities of juice, free from any admixture with other substances, can be easily obtained.

Another method devised by Pawlow for obtaining samples of juice without interference with the normal functions of the greater part of the stomach, is to make a small diverticulum representing about one-tenth of the whole stomach either at the cardiac or pyloric end. In making this diverticulum care is taken to preserve its muscular and nervous connections with the rest of the stomach, from which it is only separated by a diaphragm of mucous membrane. In a dog treated in this way it is found that the amount of juice secreted by the small

stomach always bears the same ratio to the amount secreted by the large stomach, while the digestive power of the juice from the small stomach is approximately equal to that from the large.

The gastric juice obtained in this way is a clear colourless fluid containing from 0.3 to 1 per cent. total solids, and having an acidity equal to 0.5 per cent. hydrochloric acid. If, however, it be obtained from a pyloric diverticulum, it is neutral or alkaline in reaction. Juice from the whole stomach or from the fundus has a strong digestive action on proteins. If the juice be placed in an ice-chest for twenty-four hours, it becomes turbid owing to the production of a fine precipitate. This precipitate may be collected, and represents pepsin combined with hydrochloric acid in the purest possible form in which it can be obtained.

It was shown many years ago by Richet that the secretion of gastric juice was, in all probability, reflex, and carried out by the central nervous system. Richet had occasion to observe a patient in whom complete stenosis of the œsophagus had been brought about as the result of swallowing caustic alkali, so that gastrotomy had to be performed in order to keep the patient alive. Richet noticed that as soon as the patient began to chew food there was a secretion of gastric juice. The same deduction must be drawn from Pawlow's experiments on dogs. The secretion of gastric juice begins and is carried out independently of the arrival of food in the stomach. Nor is the mucous membrane of the mouth the only region from which impulses can start to excite the secretion. If a hungry dog be merely shown food, the idea of satisfaction of appetite thus aroused is sufficient to excite a secretion as vigorous as that produced by a sham meal. In the experiment from which the following table is taken the dog was continually excited by showing it meat during a period of an hour and a half. At the end of this time the animal, which had an œsophageal fistula, was given a sham meal. It will be observed that the psychical secretion obtained during the first period of the experiment was rather greater than the secretion produced by the introduction of food into the mouth.

PSYCHICAL SECRETION OF GASTRIC JUICE. (Pawlow.)

Time.			Quantity.
8 minutes	10 cc.
4 "	10 "
4 "	10 "
10 "	10 "
10 "	10 "
8 "	10 "
8 "	10 "
19 "	10 "
19 "	8 "

SHAM FEEDING.

17 minutes	10 cc.
9 "	10 "
8 "	10 "

The afferent channels for this reflex may be therefore either the afferent nerves from the mouth, or, when the *idea* of food is involved, any of the nerves of special sense, such as sight, smell, or hearing, through which these ideas are called forth. The efferent channels can only be one of two nerves, viz.:—the vagus and the sympathetic, since these are the only two which are distributed to the stomach. That it is the former of these nerves which is involved is shown by the fact, recorded by Pawlow, that psychical secretion, as well as the results of a sham meal, are entirely abolished by division of both vagi. On this account division of both vagi may give rise to entire absence of gastric digestion, and death of the animal may ensue from inanition, or from poisoning by the products of decomposition of food in the stomach, even when care has been taken to avoid injury to the pulmonary and tracheal branches of these nerves.

The converse experiment of exciting secretion by direct stimulation of the vagus presents greater difficulties. Stimulation of the vagus in the neck causes stoppage of the heart, and consequent anæmia of the mucous membrane of the stomach. Moreover, the stomach seems to be much more susceptible than the salivary glands to the action of poisons, such as anæsthetics. Its activity is also easily affected by inhibitory impulses

arising in the central nervous system as the result of either painful impressions or emotional states of the animal. In order to avoid these disturbing factors Pawlow proceeded as follows:—An animal with fistulæ of œsophagus and stomach had one vagus nerve divided. A thread was attached to the peripheral end of the cut vagus and allowed to hang out through the wound. Four days after the operation the vagus was drawn out of the wound by carefully pulling on the thread, so as not to hurt or frighten the animal in any way, and its peripheral end stimulated by means of induction shocks. No effect was produced on the heart, owing to the degeneration of the cardio-inhibitory fibres, which is well known to occur within this period after section. Five minutes after the commencement of the stimulation the first drop of gastric juice appeared from the gastric cannula, and a steady secretion of juice was obtained with continuation of stimulation. This experiment furnishes the decisive and final evidence that the secretory nerves to the stomach run in the two vagi. There is one marked difference, however, between the action of these nerves and the action of the chorda tympani nerve on the submaxillary gland, namely, the great length of the latent period before secretion occurs. The length of this latent period has not yet been satisfactorily explained. It cannot be due to delay occurring between the vagus fibres and the local nervous mechanism in the stomach. It may be that the chemical changes finally resulting in secretion require a longer period for their accomplishment than is the case in the salivary gland. Physiologically there is indeed no special need for a rapid secretion of gastric juice, whereas in the mouth it is essential that the introduction of food should be immediately followed by the production of saliva, for the tasting and testing of the food and for its subsequent mastication or rejection.

These experiments show conclusively that an important—probably the most important—part of the gastric secretion is determined by a nervous mechanism. This nervous secretion does not, however, account for the whole of the gastric juice obtained as the result of a meal. If an animal provided with

two gastric fistulae, one into a diverticulum and the other into the main stomach, have both its vagi divided, it is found that the introduction of meat into the large stomach is followed, after a period of twenty to forty-five minutes, by the appearance of a secretion of gastric juice from the small stomach. Moreover, when an animal is given a normal meal, and is allowed to swallow the food after mastication, the total amount of gastric juice obtained is greater than that produced by the sham feeding alone, and the flow is of longer duration. In fact, we may say that the gastric juice secreted in response to a normal meal consists of two parts, viz.:—(1) a large amount, the secretion of which begins within five minutes of the taking of the food and is determined by the reflex nervous mechanism described above; and (2) a smaller portion, the secretion of which is excited by the presence of food in the stomach. This combined character of the gastric juice produced by a normal meal is shown in the following table (Pawlow):—

Hours.	Normal Meal. 200 gm. meat into Stomach.		150 gm. meat into Stomach.		Sham Meal.		Sum of 2 last experi- ments.
	Quantity cc.	Strength mm. dig.	Quantity cc.	Strength mm. dig.	Quantity cc.	Strength mm. dig.	
1	12.4	5.43	5.0	2.5	7.7	6.4	12.7
2	13.5	3.63	7.8	2.75	4.5	5.3	12.3
3	7.5	3.5	6.4	3.75	0.6	5.75	7.0
4	4.2	3.12	5.0	3.75	0	0	5.0

In the first column is given the result of a normal meal on the secretion from the gastric diverticulum. In the second column are given the amount and digestive power of the juice which is excited by the direct introduction of 150 gms. of meat into the large stomach of the animal, care being taken not to excite in any way the nervous reflex mechanism. In the third column is given the amount and digestive power of the juice which is evoked by a sham meal of 200 gms. of meat. In the fourth column is given the sum of the last two experiments. It will be seen that the total effect of the sham meal, plus the direct introduction of meat into the stomach, is almost

identical with the secretion obtained when the food is taken in a normal way and allowed to pass through the œsophagus into the stomach.

This second phase of gastric secretion, namely, that excited by the presence of food in the stomach even after section of both vagi, has been ascribed by Pawlow and Popielski to the excitation of a local nervous mechanism situated in the walls of the stomach. It is not produced by mechanical stimulation, nor by all forms of food. Thus, the introduction of white of egg, of starch solution or bread, directly into the stomach, causes no secretion. If, however, the bread be digested for a short time with gastric juice before it is introduced into the stomach, secretion is produced. There is at present no fact which would absolutely exclude the explanation offered by Pawlow and Popielski. On the other hand, certain facts observed by Dr. Edkins tend to show that this second phase of secretion is brought about by chemical rather than nervous means. Edkins' experiments were carried out in the following way. The animal, dog or cat, having been anæsthetised, the abdominal cavity was opened, and a ligature passed round the lower end of the œsophagus so as to occlude the cardiac orifice and effectually crush the two vagus nerves. A glass tube was then introduced through an opening in the abdomen into the pyloric part of the stomach, and fixed in this position by a ligature tied tightly round the pylorus. The glass tube was connected by means of a rubber tube with a reservoir containing normal salt solution at the temperature of the body. By means of this reservoir, a certain amount of fluid was introduced into the stomach and kept there at a constant pressure; the quantity of fluid introduced varied from 30 to 50 c.c. It has been shown by Edkins, as well as by von Mering, that no absorption of water or saline fluid occurs in the stomach. It is, therefore, possible to recover the whole of the fluid an hour after it has been introduced by simply lowering the reservoir below the level of the animal's body. If secretion of gastric juice has occurred into the cavity of the stomach, the fluid will be increased in amount, and will

contain hydrochloric acid as well as pepsin. In a series of control observations, Edkins showed that the mere introduction of this fluid into the stomach caused no secretion of gastric juice, the fluid removed at the end of an hour having the same bulk and the same neutral reaction as the fluid which had been injected. Edkins then tried the influence of injecting substances into the blood stream. The injection of peptone, of acid, of broth, or of dextrine into the blood stream produced no secretion of gastric juice. If, however, in the course of the hour during which the fluid was allowed to remain in the stomach, a decoction made by boiling pyloric mucous membrane with acid, or with water, or with peptone, was introduced in small quantities every ten minutes into the jugular vein, the fluid removed at the end of the hour was found to be distinctly acid in its reaction and to possess proteolytic properties. The injection of these substances had therefore caused the secretion of a certain amount of gastric juice containing both hydrochloric acid and pepsin. In order to produce this positive effect, it was necessary to employ pyloric mucous membrane, extracts made by infusing or boiling cardiac mucous membrane with any of these substances being without effect. Edkins concludes, therefore, that the secondary secretion of gastric juice is determined, not as Pawlow and Popielski imagined, by a local stimulation of the reflex nervous apparatus in the gastric wall, but by a chemical mechanism. The first products of digestion act on the pyloric mucous membrane, and produce in this membrane a substance which is absorbed into the blood stream, and carried to all the glands of the stomach, where it acts as a specific excitant of their secretory activity. This substance may be called the gastric *secretin* or gastric *hormone*. It is noteworthy that it is produced only in the pyloric portion of the stomach.

The normal gastric secretion is therefore due to the co-operation of two factors. The first and most important is the nervous secretion, determined through the vagus nerves by stimulation of the mucous membrane of the mouth, or by the arousing of appetite in the higher parts of the brain. The

second factor, which provides for the continued secretion of gastric juice long after the mental effects of a meal have disappeared, is chemical, and depends on the production in the pyloric mucous membrane of a specific substance or hormone, which acts as a chemical messenger to all parts of the stomach, being absorbed into the blood and thence exciting the activity of the various secreting cells in the gastric glands.

An important question has arisen as regards the power of the mucous membrane of the stomach to adapt its activities to the nature of the food taken. Pawlow has shown that there is a marked difference in the amount of gastric juice secreted according to the nature of the food, and that this difference in amount may be associated with moderate differences in digestive power and in acidity. These differences relate only to the gastric juice produced during the second phase of secretion, the psychical or appetite juice having always the same characters, the same digestive power, and the same percentage of hydrochloric acid whatever the previous diet of the animal has been. It is doubtful, however, whether Pawlow's results justify us in ascribing a specific sensibility to the gastric mucous membrane. The psychical juice depends on appetite, and is therefore greater in amount the more welcome the food is to the animal. On the other hand, the juice secreted in the second phase must vary according to the quantity of gastric hormone produced in the pyloric mucous membrane, if we assume the correctness of Dr. Edkins' examination. It must therefore vary with the nature and amount of the substance produced in the preliminary digestion of the gastric contents by means of the psychical juice. It seems in this way possible to explain the variations observed on different diets, such as meat and bread, without having recourse to the difficult assumption of a specific sensibility of the gastric mucous membrane to such inert substances as starch, dextrin or peptone.

2. *The Chemical Changes in the Food.*—The digestive processes carried out in the stomach of man are due, not only to the gastric juice, but also to the saliva. The food which is

taken at a meal forms a mass occupying the fundus of the stomach in which the food last swallowed occupies the central position. As we shall see in dealing with the movements of the stomach, this mass is not broken up, but is gradually dissolved from the outside by the action of the gastric juice, and the dissolved parts are pressed by the tonic contraction of the walls of the fundus into the pyloric end of the stomach, where they are subjected to the action of the "pyloric mill." The addition of hydrochloric acid, in the strength in which it is present in gastric juice, to saliva at once stops the action of the ptyalin. In the mass of food lying in the fundus, however, this penetration is only slow. If the food has been mixed with litmus, it is found that in the case of an animal, such as a cat, forty minutes to an hour may elapse before the litmus in the centre of the mass is reddened. During the whole of this time, therefore, the greater part of the food, moistened and thoroughly mixed with saliva, is kept in the fundus of the stomach at the temperature of the body, so that opportunity is afforded for the action of the ptyalin to proceed to a very considerable extent. A very large proportion of the cooked starch taken in a meal is converted into dextrine or maltose by the action of saliva in the stomach itself.

The actions of the gastric juice itself on the food-stuffs are due, partly to the acid, partly to the combined action of the acid and the ferments of the juice. The acid of the gastric juice obtained in the way described in the last section is practically entirely hydrochloric acid. When, however, we examine the gastric contents, as, *e.g.*, of a test meal composed of a mixture of gastric juice and some digested food, we always find other acids present, among which the most prominent is lactic acid. So constantly is this latter acid present that it was formerly thought by some physiologists to be the chief acid of the gastric juice. It is, however, produced, not by secretion from the glands, but by processes of fermentation occurring in the food. Whenever we take carbohydrates we swallow at the same time micro-organisms, and these in the warm moist mass quickly

attack the carbohydrates, converting them into sugar and lactic acid. As the gastric juice gradually soaks into the food and renders it acid, it stops this lactic acid fermentation, so that whereas in the early stages of gastric digestion both acids are present in considerable quantities, towards the end of gastric digestion lactic acid is almost entirely absent.

By the action of the hydrochloric acid certain changes are induced in the food-stuffs. Cane sugar is inverted to glucose and fructose; some proteins, such as blood fibrin, are swollen up to form a jelly-like mass. The caseinogen of milk is precipitated, the collagen of the connective tissues is swollen up. It is possible that a certain small amount of hydrolysis also takes place in the dextrine and maltose produced by the action of ptyalin on starch.

The chief digestive function of the gastric juice is, however, dependent on the action of the ferment pepsin. This substance, which is inactive in neutral medium, needs the co-operation of an acid, hydrochloric acid being the most effective, though its place may be taken by phosphoric, sulphuric or lactic acids. Its main effect is on the proteins of the food. The stages in its action may be best studied by taking as an example its action on blood fibrin. If fibrin be immersed in 0.4 per cent. hydrochloric acid, it swells up to a gelatinous mass. On then stirring in an extract of gastric mucous membrane, or any preparation of pepsin, the gelatinous mass rapidly undergoes solution. If the mixture be boiled and neutralised immediately after solution has occurred, the whole of the protein is thrown down in a coagulated form.

The chief effect, therefore, is the production of coagulable soluble proteins from the insoluble fibrin. If the action be allowed to proceed for some hours, a whole series of products of hydrolysis are found in the mixture. On neutralising the fluid, a precipitate may be thrown down consisting largely of acid albumen. The greater portion of the protein, however, remains in solution. This remainder may be purified from any unalterable coagulable proteid by boiling in slightly acid solution

and filtering. The filtrate contains a mixture of bodies belonging to the class of hydrated proteins. The whole classification of these hydrated proteins is an arbitrary one, depending on their relative solubility in salt solutions. By means of fractional precipitation with ammonium sulphate or zinc sulphate, these substances can be still further subdivided. The following table represents the chief bodies obtained by Pick by means of this method from Witte's peptone, a commercial preparation containing albumoses and peptones:—

FRACTIONAL SEPARATION OF WITTE'S PEPTONE.

Am_2SO_4		Hydrolysis.
1. $\frac{1}{2}$ sat.	Primary albumoses— Hetero-albumose insoluble in alcohol	Tyrosine 89 per cent.
	Proto-albumose soluble in alcohol 80 per cent (Kühne)	Leucine and glycine, 25 per cent.
2. $\frac{2}{3}$ sat.	Deutero-albumoses— A.—Insoluble in alcohol. Thio-albumose	Cystine.
	Soluble in alcohol, gives Millon's reaction	Tyrosine.
3. $\frac{1}{4}$ sat.	B.—1. Insoluble in alcohol 65 per cent. (sulphur)	Cystine.
	2. Insoluble in alcohol 75 per cent. (glycalbumose)	Carbohydrate.
	3. Soluble in alcohol (Millon); (a) Insoluble in acetone; (b) Soluble in acetone, not ether.	
4. $\frac{1}{8}$ sat. acid	C.—	
5. KI_3	Peptone A. Insoluble in alcohol	Carbohydrate.
6. KI_3	Peptone B. Soluble in alcohol	No carbohydrate

Although it is impossible to ascribe absolute chemical individuality to each of the products isolated by means of fractional salt precipitation, the results obtained by Pick, and represented in the third column of the table, by hydrolysis of these different

bodies, show that in the breakdown of protein produced by gastric juice there is really a division of the complex molecule into smaller molecules, which are qualitatively different. Thus, of the fractions which he obtained, some contain the greater part of the sulphur originally present in the protein molecule, another contains the greater part of the carbohydrate group, while others are free altogether from the tryptophane group which is responsible for Hopkins' reaction obtainable in the original protein.

Proceeding from primary through secondary albumoses to peptones, there is probably a continuous diminution in the size of the molecule. During the time which gastric juice has to exert its influence, a maximum, say, of twelve hours, the breakdown of proteins never passes beyond the albumose and peptone stage, and it is in this form that the proteins of the food pass on through the pyloric orifice into the small intestine.

Action on the Connective Tissues.—The connective tissues are made up chiefly of white fibres, more or less modified, which consist of collagen. This substance forms the main basis of areolar tissue, of white fibrous tissue, and of bone. On prolonged boiling it is converted into gelatine. The gastric juice dissolves collagen, converting it probably through the stage of gelatine into gelatoses and gelatine peptones, bearing the same relation to the original substance as is borne by the albumoses and peptones to the proteins.

On account of this action, adipose tissue (which consists of protoplasmic cells distended with fat, and bound together by connective tissue) is broken up into its constituent cells. The protoplasmic pellicle is dissolved, and the fat floats freely in the gastric juice.

Elastin, which also occurs in varying amounts as the chief constituent of the elastic fibres of connective tissues, is slowly acted upon by gastric juice. Under the conditions of natural digestion, however, it may be regarded as indigestible.

Mucin, which forms a considerable proportion of the ground substance of connective tissues, is converted by gastric juice into peptone-like substances and into reducing bodies probably allied to glycosamin.

The nucleo-proteins, the chief constituents of cells, and therefore ingested in large amounts with such food-stuffs as sweet-breads, are first dissolved by the acid of the gastric juice, and are then broken up. The protein half is converted into albumoses and peptones, while the nuclein moiety is precipitated in an insoluble form.

On phospho-proteins gastric juice acts in a somewhat similar manner. The protein of milk, caseinogen, undergoes special changes in the stomach. The first effect of gastric juice, even in neutral medium, is to convert the caseinogen into an insoluble casein. This action is generally ascribed to the presence of a distinct ferment of the gastric juice named rennin, or rennet ferment. But according to some authorities it is due directly to the pepsin, *i.e.*, rennin and pepsin are identical.

For the conversion of caseinogen into the solid clot of casein, the presence of lime salts is necessary. The addition of rennet to an oxalated milk apparently produces no effect, but clotting ensues if a soluble lime salt, such as calcium chloride, is then added to the mixture. Under the action of the acid gastric juice, the solid clot of casein is dissolved, but a precipitate is left containing a considerable proportion of the original phosphorus of the caseinogen. This precipitate is sometimes spoken of as para-nuclein, or pseudo-nuclein. It does not yield the typical purin bases on hydrolysis with acids, but contains phosphoric acid in organic combination. By prolonged digestion with strong gastric juice it is possible to dissolve up practically the whole of this precipitate. It is therefore thought that in the clotting of milk the caseinogen, under the action of the rennet, first undergoes a conversion into a soluble casein and some other globulin-like body. The soluble casein, then, under the influence of the lime salts, forms an insoluble casein which is precipitated, and causes the solidification of the milk. In the absence of lime salts the splitting of caseinogen takes place, but the second stage of the process cannot occur until the lime salts are added.

Effect on Carbohydrates.—On account of the fact that cane sugar undergoes inversion into equal molecules of glucose and

fructose in the stomach, it has been sometimes thought that gastric juice contains the ferment invertase. It seems, however, that the inversion which takes place in the stomach can be completely accounted for by the action of the hydrochloric acid present, and that there is no need to assume the presence of a special ferment. In the same way, inulin, the variety of starch which gives rise to the lævorotatory fructose on hydrolysis, and is found in dahlia tubers and certain other reserve structures of plants, is converted by the acid of gastric juice into fructose. The inulin is, therefore, completely utilised in the alimentary canal of animals, although there is no definite ferment inulase provided for its hydrolysis.

Effect on Fats.—The chief effect of gastric juice on fats is the solution of their connective tissue framework and protoplasmic envelopes, so as to set the fat free in the stomach contents. After a fatty meal it is found, however, that a considerable proportion of the fat in the stomach has undergone hydrolysis, and that a large proportion of it is present in the form of free fatty acid. In this hydrolysis two factors are involved: (1) the action of the warm dilute hydrochloric acid; (2) the action of a special fat-splitting ferment or lipase, which is secreted by the walls of the stomach, and acts especially at the beginning of gastric digestion, before the contents have attained a high degree of acidity. The chief digestion of fat takes place, however, in the next segment of the alimentary canal, namely, in the duodenum.

3. *The Movements of the Stomach.*—When a meal is taken, the inhibition which precedes the passage of each bolus spreads to the whole stomach wall, so that any movements which have been present before the meal come to an end, and the stomach is in a relaxed and passive condition to receive the food passing to it from the mouth. The food passes into the large fundus of the stomach and accumulates there as a compact mass. The stomach remains passive for some time after the beginning of a meal, and, as a rule, it is not until twenty to thirty minutes later that the first movements make their appearance. Secre-

tion of gastric juice commences even while the food is in the mouth. The acid juice cannot, however, penetrate the great mass of food lying in the fundus, and in the interior of this mass salivary digestion can go on from thirty minutes to one and a half hours after the food has been swallowed. A very considerable portion, therefore, of the salivary digestion occurs in the stomach itself. For the understanding of the subsequent movements of the stomach wall it is important to remember its functional division into two parts, namely, fundus and pyloric end or antrum. Although the dead stomach appears to form one sac, observation of a stomach recently removed from the living animal and placed in warm salt solution shows distinctly this division into two parts, namely, a tubular part at the pyloric end, and a bag-like portion forming four-fifths of the stomach at the cardiac end. The division between the two is marked by what has been called the "transverse band" of the stomach, a region where there is almost always contraction of the circular muscle fibres. So marked is this in the living stomach that one would expect on dissection to find evidence of sphincter-like thickenings at this point. It is, however, a physiological and not an anatomical condition.

The movements of the stomach can be best studied by Cannon's method, that is, by direct observation of the movements in a living unanæsthetised animal by means of the Röntgen rays. In order to make the shape of the stomach visible, the food—bread and milk—is mixed with a quantity of bismuth sub-nitrate. The presence of this salt does not interfere with the processes of digestion, but renders the gastric contents opaque to the Röntgen rays. On examining by this means the stomach of a cat which has just taken a meal, the whole of the food is seen to be lying in the fundus. It is marked off by a strong constriction of the transverse band from the antrum. In about twenty to thirty minutes faint waves of contraction begin a little to the cardiac side of the transverse band and travel slowly towards the pylorus. These waves succeed one another, so that the pyloric part of the stomach may present a series of constrict-

tions. The effect of these waves is to force the food which has been digested by the gastric juice and detached from the surface of the mass of food in the fundus towards the pylorus. The pylorus remaining closed, the food cannot escape, and therefore is squeezed back, forming an axial reflux stream towards the cardiac end. These contractions last throughout the whole period of gastric digestion, and become more marked as digestion proceeds. Their effect is to bring the whole of the food in close contact with every particle of pyloric mucous membrane, and to cause a thorough mixture of food and gastric juice. At varying periods after a meal, according to the nature of the food taken, the arrival of one of these waves of contraction at the pylorus causes a relaxation of this orifice, and a few cubic centimetres of gastric contents are squirted into the first part of the duodenum. While these movements of the pyloric mill are going on, the cardiac portion of the stomach is exercising a steady pressure on its contents in consequence of a tonic contraction of its muscular wall, so that each successive portion of the food mass which is loosened by the digestive action of the gastric juice is forced on into the pyloric mill. As digestion proceeds, the opening of the pylorus becomes more frequent. The stomach empties itself more and more until finally the whole of the viscus has the shape of a curved tube. At the very end of digestion the pylorus may open to allow the passage even of undigested morsels of food.

The foregoing description applies especially to the events which succeed the taking of a considerable meal. If warm fluid alone, *e.g.*, water, be swallowed, the opening of the pylorus occurs within a very short time after the fluid has reached the stomach. Thus, if a large draught of water be taken to quench thirst it may arrive in the duodenum within a minute or two after being swallowed, and it is from the duodenum and small intestine that any absorption takes place. When a meal is undergoing digestion there seems to be a distinct relation between the amount of acid present in the gastric contents and the opening of the pylorus. One may indeed say that acidity

of the gastric contents exercises a direct inhibitory stimulus on the pyloric sphincter.

These movements of the two portions of the stomach may be observed also on anæsthetised animals, and even on a stomach which has been excised and placed in warm salt solution. They must, therefore, have their origin in the walls of the stomach itself. Although the co-ordination between the two parts of the stomach, between the tonic contractions of the fundus and the rhythmic contractions of the antrum, may be carried out by the local nervous system—Auerbach's Plexus—situated between the layers of the muscular coat, it is probable that the advancing waves of contraction observed in the antrum are myogenic, *i.e.*, directly originated in and determined by the muscle fibres themselves. Although we have no direct evidence that these movements persist after throwing the local nervous system out of action, it is evident that they do not partake of the nature of a true peristalsis, since they are not preceded by a wave of relaxation. The opening of the pylorus, on the other hand, which occurs at increasingly frequent intervals at the end of a wave must be ascribed to a nervous mechanism. Although the local mechanism probably plays the greater part in this act of relaxation, there is no doubt that the normal emptying of the stomach is also largely dependent on the integrity of the connection of this viscus with the central nervous system. If both vagus nerves be divided in a dog below the point at which they give off their branches to the lungs and heart, it is found that a large amount of food remains in the stomach in an undigested condition. The secretion of gastric juice is deficient, and the opening of the pylorus is not easily carried out. Such dogs, therefore, tend to die of *sapræmia*, being poisoned by the absorption of products of putrefaction from the gastric contents. Pawlow has shown that animals can be kept alive for months after division of both vagi if a gastric fistula be made, the animals be carefully fed, and care be taken to wash out adherent non-digested portions of food from the stomach.

The opening of the pylorus depends not only on intragastric events, but also on the condition of the duodenum. It has been shown by Serdjukow that the pylorus remains firmly closed so long as the contents of the duodenum are acid. If alkaline fluid be introduced into the stomach, this is rapidly passed into the duodenum. If, however, some acid be introduced at the same time into the duodenum by means of a duodenal fistula, the pylorus remains firmly closed, and no fluid passes into the duodenum until the acid which was placed there has been neutralised by the secretion of pancreatic juice and succus entericus. We have probably in the walls of the alimentary canal a local nervous mechanism for the movements of the pyloric sphincter. This may be played upon by impulses starting either in the stomach or in the duodenum, probably by the contact of acid with the mucous membrane. Increasing acidity on the side of the stomach causes relaxation of the orifice, whereas acidity on the duodenal side causes contraction of the pyloric sphincter. The exact parts played in this mechanism by the local system and by the central nervous system respectively have not yet been thoroughly made out, though there is no doubt that these movements may proceed independently of any connection with the central nervous system.

Stimulation of the peripheral end of the vagus nerves may exercise varying effects on the stomach wall as well as on its sphincters. In the normal animal, stimulation of the peripheral end of the vagus, as a rule, causes strong contractions of the œsophagus as well as of the cardiac sphincter. After the administration of atropine, stimulation of the same nerve will occasion dilatation of the cardiac sphincter. On both cardiac and pyloric portions of the stomach the vagus exercises inhibitory as well as augmentor effects. So far as concerns the musculature of the fundus the most usual effect is an inhibition during stimulation of the vagus succeeded by an augmented tonus immediately the stimulus is removed. If the vagus be excited a number of times, the tonus of the muscular wall augments with each stimulus. On the pyloric portion stimulation of the

vagus also causes inhibition followed by contraction. The inhibition may, however, be very short and in rare cases altogether absent, so that during the excitation this inhibition is followed by a series of large rhythmic contractions. The prevailing motor effect of the vagus, therefore, is in the fundus increased tonus, in the pyloric portion augmented peristaltic waves. On the pylorus we may obtain from vagal stimulation either increased or diminished contraction. The conditions under which each of these may be evoked have not yet been definitely ascertained. Whether the splanchnic nerve, *i.e.*, the sympathetic system, has a direct influence on the movements of the stomach, has been disputed. From my own experiments I concluded that any effect produced by stimulation of this nerve, generally consisting in diminished motor activity, is probably due to the simultaneous influence on the vascular supply to the organ; the blood vessels being constricted, an artificial anæmia is produced, which in itself is sufficient to account for diminished activity. Other observers regard the splanchnic as having an influence on the stomach similar to its action on the intestine, and regard it as the chief inhibitory nerve to this organ. It is possible that the extent to which the stomach is brought under the control of the sympathetic system may vary in different species of animals.

PART IV.

DIGESTION IN THE INTESTINES.

As the mixture of the gastric juice and the partially digested food-stuffs, the chyme, passes through the pylorus into the duodenum, it comes in contact with a number of different juices, namely. the pancreatic juice, the secretion of Brunner's glands, the bile and the intestinal juice produced from the crypts of Lieberkühn. Since these juices are poured out simultaneously

as the food enters the duodenum, and in proportion to the amount of chyme which passes the pylorus, we shall have to consider their joint action on the constituents of the food which have undergone partial digestion in the stomach. It will be convenient, however, in discussing the mechanism of secretion of these juices to deal with each one separately, and to see how far their co-operation in the processes of digestion is secured by identity of mechanism.

(a) *Pancreatic Juice*.—In order to study the secretion of the pancreatic juice, the course of its duct or ducts must be diverted or a cannula inserted so as to lead the secretion to the outside of the body where it may be collected. In man, as in most of the higher mammals, the pancreas is provided with two ducts, one of which generally opens with the bile duct on a common papilla. In man and in the cat this latter is the larger of the two. In the rabbit the main duct opens a considerable distance below the opening of the bile duct. In the dog the larger duct opens into the duodenum about one inch below the point of entry of the bile duct. It is easy at this point in the dog to insert a cannula, but until recently no effective means was known of exciting a secretion from such a temporary fistula. Most of our knowledge with regard to the time relations of the secretion of pancreatic juice has been derived from the study of permanent fistulæ. The first physiologist to establish a permanent fistula of the pancreas was De Graaf, who collected in this way a certain amount of juice, but failed to recognise its digestive properties. Claude Bernard tied a metal cannula in the larger duct in the dog. One end of the cannula projected from the abdominal wall, and was armed with a rubber bag to collect the secretion. In most cases, however, the cannula became loose and dropped out within a few days, and the animal recovered with restoration of a passage from the occluded duct into the intestine. Pawlow, employing a method first suggested by Heidenhain, cuts out a quadrangular piece of the duodenal wall, including the papilla on which is situated the orifice of the pancreatic duct. The

wound of the intestinal wall is closed by sutures, and the quadrangular piece is brought to the surface of the abdominal wound, so that any discharge from the pancreatic duct will flow out on the surface of the body. This operation is easy to carry out, and with proper care is invariably attended by recovery. The after-care of the animals, however, requires great attention. Not only do they suffer from the loss of pancreatic juice, but the juice which is secreted acquires, as it flows over the mucous membrane surrounding the papilla, strong digestive properties, so that it tends to cause ulceration of the surrounding skin. Moreover, the duct in this abnormal situation tends to become infected, and we may thus have a condition of pancreatitis produced by the infection ascending the duct to the gland itself. By diminishing the amount of meat given to the animals and by the administration of sodium bicarbonate, the amount of juice secreted can be reduced to a minimum. By scrupulous cleanliness, and by taking care to collect the juice as it is secreted without allowing it to flow over the adjacent parts of the abdominal wall, it is possible to prevent ulceration and the subsequent infection of the duct itself, and Pawlow has succeeded in keeping dogs alive for several years in excellent condition in spite of the presence of a pancreatic fistula.

In such an animal it is easy to study the normal relation of the secretion of pancreatic juice to the process of digestion. It is found that shortly after taking food into the stomach (five to twenty minutes), a flow of pancreatic juice commences. This secretion lasts for about five hours after a meal, and is generally most pronounced during the third hour, *i.e.*, the time at which food is passing in largest quantities from the stomach into the duodenum. The following experiment by Pawlow shows the amount of pancreatic juice secreted after the ingestion of 600 c.c. of milk. A meal of meat and bread would induce a secretion three or four times as great as that produced by the milk.

PANCREATIC SECRETION AFTER A MEAL OF 600 C.C. MILK.

TWO EXPERIMENTS.

Hour after Feeding.					Quantity of Juice in c.c.			
1st	8.75	8.25
2nd	7.5	6.0
3rd	22.5	23.3
4th	9.0	6.25
5th	2.0	1.5
Total					49.75	45.3

It is evident that the stimulus of the secretion of pancreatic juice is afforded by the entry of the gastric contents into the duodenum. In a study of the effect produced by various substances on pancreatic secretion, Pawlow found that whereas a small secretion could be induced by the introduction of water through the stomach into the duodenum, a larger secretion was produced by the introduction of oil, and a still larger secretion by the introduction of 0.4 per cent. hydrochloric acid. Pawlow regarded the acidity of the chyme, therefore, as the most essential factor in exciting the secretion, and used the introduction of hydrochloric acid as a routine means of inducing the flow of pancreatic juice when he required any of this fluid for examination. In searching for the seat of stimulation, Dolinski, one of Pawlow's pupils, found that the presence of acid in the stomach itself had no influence on the pancreas, but that the activity of this gland might be excited by the introduction of acid directly into the duodenum or into the upper part of the small intestine. The effect, however, diminished the lower down in the gut the acid was injected. If it were introduced into the last foot of the ileum, no secretion was obtained. Pawlow, in common with the previous workers on the subject, came to the conclusion that the secretion of pancreatic juice under these conditions was a reflex secretion analogous to that obtained from the salivary glands when acid is introduced into the mouth. Bernard had previously shown that a flow of pancreatic juice could be provoked by the introduction of ether into the intestine, but was unable to throw any light on the path of

the assumed reflex. Heidenhain, who devoted special attention to this point, was unable to produce any secretion by stimulation of the vagus or splanchnic nerves, though in a few cases some secretion was obtained on stimulation of the medulla oblongata. Pawlow ascribed this failure of early experimenters to the lack of observance of physiological conditions. As in the case of the stomach, he stated that it was necessary to operate on an animal unpoisoned by anæsthetics, and with a normal blood supply to the gland, and yet to maintain the animal free from pain or discomfort, which might reflexly inhibit the activity of the gland. In a dog with a permanent pancreatic fistula, Pawlow divided one vagus and left the divided end in the wound for four days. At the end of this time the peripheral end of the nerve could be pulled out of the wound without causing the dog any pain or discomfort. The cardio-inhibitory fibres were degenerated. Stimulation of the peripheral end of the nerve, however, evoked secretion of pancreatic juice. In the same way a secretion was obtained after section of the spinal cord in the neck and stimulation of the vagus nerve in the thorax below the point at which it had given off its cardio-inhibitory fibres. In a few cases secretion was obtained on stimulation of the splanchnic nerves, and Pawlow therefore regarded the secretion as determined either reflexly or psychically through the cortex by impulses leaving the central nervous system and travelling to the gland along one of these two sets of nerves.

It is worthy of note, however, that the secretion obtained by stimulation of either of these nerves never approaches in amount that which may be produced by the injection of acid into the duodenum or ileum, and the interaction of the vagi in this so-called acid reflex was put out of court when it was shown independently by Wertheimer in France and by Popielski in Russia that the effects of an introduction of an acid into the duodenum were unaltered even after section of both vagus and splanchnic nerves and destruction of the sympathetic ganglia of the abdomen. Both these observers, nevertheless, adhered to the essential nervous nature of the reaction, and ascribed it to the

intervention of the local nervous system present in the form of the plexuses of Auerbach and Meissner in the walls of the gut, and as collections of ganglion cells in the substance of the pancreas itself. It was with a view of studying this local reflex that I took up the question of the formation of pancreatic juice, but very soon obtained evidence which rendered the views of the observers just quoted untenable. Having found that the introduction of acid into a loop of jejunum caused a secretion of pancreatic juice, I proceeded to ligature the two ends of the loop and to extirpate the whole of the abdominal ganglia and all the nerve plexuses surrounding the large vessels, and especially those on the vessels going to the loop in question. The loop was, therefore, entirely separated from the rest of the body, except by means of its blood supply. The introduction of 0.4 per cent. hydrochloric acid into the loop, however, caused within two to three minutes a secretion of pancreatic juice equal in amount to that obtained after the introduction of acid into a loop which was still in nervous connection with the rest of the animal. Since in this case the only connection of the loop with the pancreas was by means of the circulation, the message arousing the activity of the latter must have travelled by the blood and not by the nervous system, *i.e.*, must have been of the nature of a substance and not of a mechanical change in a nerve fibre. The special messenger could not be the acid itself, since introduction of acid into the portal vein does not cause any activity of the pancreas. We are thus faced with the fact that introduction of acid into the lumen of the gut separated from the blood vessels by a single layer of intestinal epithelium produces pancreatic secretion, whereas introduction of acid without the intervention of this epithelium has no such effect. The only conclusion to be drawn from these results was that the special messenger is manufactured in the epithelial cells whenever these are acted upon by acid. This conclusion was at once confirmed on putting it to the test of experiment. A scraping of intestinal epithelial cells rubbed up with 0.4 per cent. hydrochloric acid, roughly filtered, and introduced into the blood

stream, was found to evoke a secretion of pancreatic juice larger in amount than that obtained by the introduction of acid into the gut, and within a period of fifty seconds after the injection. The special messenger, or "*hormone*," produced in this way, has received the name of *secretin*. It is not a ferment, since it is not destroyed by boiling. The most convenient method of preparing the secretin is to scrape off the mucous membrane from the upper two or three feet of the small intestine and pound it up with sand. It is then boiled with 0.4 per cent. hydrochloric acid. When the mixture is boiling, caustic alkali is added until the mixture is just slightly acid. All the coagulable proteins are thus thrown down, and on filtering, a clear fluid is obtained which contains the secretin. This body has not yet been isolated. We know, however, that it is diffusible, that it is soluble in alcohol or alcohol and ether, and that it is not precipitated by the ordinary precipitants of proteins or of alkaloids. Though readily oxidised, and therefore extremely unstable in alkaline solutions, it may be kept for weeks in gastric juice or in fairly strong acid solutions. It may be obtained from the mucous membrane either by the action of acids or by simply boiling with water, and Fleig has shown that a similar or identical body may be obtained by extracting the mucous membrane with solutions of soap. Although secretin is readily soluble in cold water or alcohol, treatment of the mucous membrane with either of these fluids does not extract any secretin. We may therefore conclude that the epithelial cells lining the gut do not contain secretin, but a precursor of this body, which we may term *pro-secretin*. Pro-secretin is insoluble in water, alcohol or salt solution, but under the action of acids, and possibly of soaps, it undergoes hydrolysis with the formation of a new body, namely, secretin. That secretin is actually responsible for the so-called reflex secretion obtained by the introduction of acid is shown by the fact that, whereas acid extracts of the duodenum yield strong solutions of secretin, the strength of the extract diminishes as we descend the gut, and an extract made from the last foot of the ileum is entirely

without effect. It will be remembered that introduction of acid into this part of the ileum is also inefficacious to produce secretion of pancreatic juice. It is interesting to note that secretin seems to be one and the same substance whatever animal it is obtained from. Thus, a solution may be prepared from the upper part of the intestine of any vertebrate, and will produce a flow of juice on injection into the veins of any animal. I have tested in this respect the monkey, dog, cat, rabbit, fowl, frog and toad, and have obtained active solutions of secretin from all these animals, as well as from man, the dog-fish, the salmon and the tortoise.

We have here an example of a type of mechanism which probably plays an important part in the correlation of activities of many organs of the body. In the normal life of the higher animals, which must be considered as a continuous series of reactions to changes in the environment, ending only with the death of the animal, those reactions, which are carried out through the intermediation of the nervous system, play such a preponderant part, that we have almost forgotten the possibility of other means of mutual adaptation among the different organs of the body. Yet, in the lowest organisms, before the appearance of any central nervous system, it is by chemical means that any co-ordination of function is determined, either among the different organisms of a colony, or among the various cells making up a multicellular organism such as the sponge. In this case the mechanism, which determines the movement of phagocytic cells towards an irritant, the chase of food, the escape from noxious environment, or the approach of sexual cells, has been given the name of chemiotaxis. Since the application of these chemical stimuli depends on their diffusion through the medium bathing the cells, the process is necessarily a very slow one. So far as the communication of one cell with another in the same organism is concerned, the process could be quickened by the circulation of a common nutrient fluid such as the blood. Before the appearance of a vascular system, however, we find that the need for quick reactions has determined the setting

apart of special reactive cells, endowed with a sensibility above that of their fellows, and united with the surface and the various tissues of the body by strands of protoplasm, specially endowed with conducting powers (nerve fibres). The whole history of the evolution of the higher types of animal henceforward centres about this nervous system. It is only in respect of the complexity of his nervous reactions that man himself has any advantage over the lower animals or plants. The development of a special nervous system, adapted for the carrying out of quick reactions to changes in the environment, has not abrogated the more lowly and primitive method for co-ordinating the activities of different parts of the body. Where the necessity does not exist for a specially rapid reaction, as, for instance, in the adaptation of the activities of the digestive glands to the presence of food in the alimentary tract, one might expect to find, as we have found, that the connection between the part of the body receiving the stimulus and the part of the body which has to react to the stimulus should be by chemical means. Of these chemical messengers, or hormones, as they may be termed (from *δρμαος* arouse or excite), we already know several examples, *e.g.*, those determining gastric and pancreatic secretion. I shall later bring forward evidence for the existence of similar bodies which determine the secretory activity both of the liver and of the intestinal glands. The suprarenal bodies manufacture in their medulla a substance—adrenalin—which, travelling over the whole body, seems to be a necessary condition for the excitation of any sympathetic nerves. In the absence of this substance there is a fall of blood pressure which is fatal within a very short time. The thyroid gland, in the same way, manufactures some substance, perhaps thyro-iodin, which is necessary for the proper growth of the tissues of the body, and especially for the discharge of the cerebral function. The foetus during pregnancy appears to secrete into the maternal blood some chemical substance which excites the growth of the mammary glands. It is probable that with increasing knowledge the list of these messenger

substances will be largely extended, and that, with their isolation, we shall have at our command means of influencing the growth and activity of the majority of the organs of the body. It is worthy of note that these substances do not belong to the group of physiologically active agents of complex and indefinite chemical composition, such as the ferments and toxins, but are, in all probability, well-defined chemical substances, highly unstable in most cases, but capable of analysis and, in some cases, at any rate, of artificial synthesis. They are comparable in many respects to the alkaloids and other substances of definite chemical composition, which form the drugs of our pharmacopœia. The practice of drugging would seem therefore to be, not an unnatural device of man, but the normal method by which a number of the ordinary physiological processes of the organism are carried out.

I have compared the action of the secretin and other hormones with that of drugs. There seems, however, to be one essential point of difference between these two classes of bodies. If a drug such as morphine, or pilocarpin, or caffeine, or strychnine be introduced into the body, it undergoes a certain distribution determined by the varying avidity of different kinds of cells for the drug in question. Although the attachment of the drug to the different tissues may be regarded as responsible for the action of the drug, the attachment is unstable, and sooner or later a considerable portion of the drug is excreted, unchanged, or with slight modification, in the urine or into the alimentary tract. If the excretion be rapid, the drug must be given in repeated doses to maintain its effect. If the excretion be slow, the effect of repeated doses is cumulative. The two hormones with which we are best acquainted, namely, adrenalin and secretin, are distinguished by the extreme ease with which they undergo oxidation in neutral or alkaline media. It is impossible, therefore, that they should circulate in the alkaline fluids of the body without undergoing destruction, and we find accordingly no traces of substances in the urine after their injection into the blood stream. A cumulative effect is

impossible from their administration, and in order to maintain their physiological influence they have to be continually passed into the blood in small quantities. According to Dixon and Hamill, destruction by oxidation is not the only means by which these substances are caused to disappear from the body. They state that their physiological effect—*e.g.*, the action of pancreatic juice after the administration of secretin—is due to actual chemical interaction between them and the protoplasm of the cell. In a series of experiments on the pancreas they found that solutions of secretin added to suspensions of pancreatic cells caused an actual liberation of the ferments or pro-ferments contained in the protoplasm of the cells. Such a secretory process obtained *in vitro* would, *if true*, be of extreme interest for the study of intra-cellular chemical processes. I therefore repeated their experiments, but to my regret entirely failed to confirm their conclusions. Extracts of pancreas were made with water, salt solution, or solutions of secretin, and when filtered yielded fluids of exactly the same destructive power either for proteins, starches or fats. It is very easy in this experiment to obtain divergence between the strengths of various extracts according to the amount of solid matter or suspended cells which may pass through the filter paper, or according to the reaction or salt content of the fluid. I cannot, therefore, help thinking that the results obtained by Dixon and Hamill were derived from selected experiments, and that if they had had more careful equalisation of conditions in their experiments they would not have published their results. We are therefore bound to conclude that for secretin to exert its action the pancreatic cells must be in a normal living condition, and that the disturbance of this condition produced by crushing and suspension in water or salt solution suffices to check any interaction between the secretin and the precursors of the pancreatic ferments bound up in the protoplasm of the cells.

The question finally arises whether the results I have obtained can be regarded as entirely annulling the explanation given by Pawlow. Is the chemical mechanism the only means employed

in the body for the excitation of pancreatic secretion, or can the vagus also act as a secreto-motor nerve to this gland? Many conditions which give rise to pancreatic secretion, and which have been regarded as reflex in character, can be shown to be dependent on the formation of secretin. Thus there are several substances which produce pancreatic secretion when introduced into the intestine, but do not form secretin when rubbed up with the mucous membrane. Among such substances I may mention oil, and irritants such as oil of mustard. The action of oil may possibly be due to the formation of soap at the surface of the mucous membrane, and the action of this soap in producing secretin. In the case of oil of mustard, Wertheimer has shown that, if this substance be introduced into a loop of intestine and the blood from this loop be led into the veins of a second dog, a flow of pancreatic juice occurs in the latter, showing that the blood flowing from the loop contains secretin. We thus see that secretin may be produced in the cells not only as a result of the action of acid, but also in consequence of stimulation of the cells themselves. There can be no doubt that in the earlier experiments in which Pawlow obtained secretion of pancreatic juice from stimulation of the vagus, the actual excitant was secretin. The normal effect of stimulating the vagus is to cause movements of the stomach and relaxation of the pylorus. As a result there is a flow of the acid contents of the stomach into the duodenum, and the contact of these contents with the mucous membrane will give rise to the production of secretin. Pawlow has lately repeated his experiments, but taken care to prevent any possibility of escape of stomach contents into the duodenum. Under these circumstances a flow of juice is obtained, but the flow is so minimal that it has to be measured in a capillary tube, and at the end of two or three hours' stimulation of the vagus the total result may be 2 or 3 c.c. of juice. When secretin is injected for a similar length of time, we obtain from a moderate-sized dog between 50 and 100 c.c. The action of the nervous system on the pancreas is, therefore, minimal, and we must ascribe almost the whole

of the secretin obtained during digestion as dependent on the chemical mechanism I have just described.

Properties of the Pancreatic Juice.—The juice obtained from a temporary pancreatic fistula by the injection of secretin into the blood stream resembles in all points that which may be obtained from an animal with a permanent pancreatic fistula as a result of the ingestion of food. It is a clear colourless fluid, somewhat viscid, with a specific gravity of about 1030. It contains 1.2 to 2.5 per cent. total solids, of which about 1 per cent. consists of salts, and the remainder generally of coagulable proteins. About half the proteins are precipitated on neutralisation. The juice is strongly alkaline, 10 c.c. of juice requiring for their complete neutralisation between 10 and 15 c.c. of decinormal acid.

The alkalinity of the pancreatic juice corresponds almost exactly to the acid of the gastric juice. Thus in one experiment 70 c.c. of pancreatic juice required for their complete neutralisation 78 c.c. of 0.4 per cent. hydrochloric acid. Comparative analyses have been carried out by Mr. Zilwa of juice obtained after the injection of secretin and that obtained after administration of pilocarpin. His results are contained in the following tables:—

	A.	B		C.	D	
Alkalinity:—		(a)	(b)		(1)	(12)
No. of c.c. $\frac{N}{10}$ NaOH equal to 10 c.c. juice i.e., in terms of Na in 100 c.c.	12.7 ·2921	12.4 ·2852	9 ·2587	5.5 ·1166	13.15 —	·14 —
Total solids in 100 c.c.	1.6 1.56	2.25	1.15	$\left\{ \begin{array}{l} 6.38 \\ 6.40 \end{array} \right\}$	1.62	1.04
Total proteins	0.5	—	—	4.08	.63	Coagulum under 55° C. = .38. Coagulum between 55° and 75° = .19. Opacity over 75° = .98.
Ash	$\left\{ \begin{array}{l} 1.00 \\ 0.92 \end{array} \right\}$	1.00	1.00	1.3	1.00	—
Chlorides	$\left\{ \begin{array}{l} .2808 \\ .2966 \end{array} \right\}$	—	—	·2695	—	—
Total nitrogen	—	—	—	·735	—	—

- A. Secretin juice from 3 dogs. Sp. gr. 1014. February 11th, 1903.
 - B. Secretin juice. Specimen collected at beginning (a), and at end (b).
March 11th, 1903.
 - C. Pilocarpin juice. May 8th, 1903.
 - D. Secretin juice collected in successive 10 c.c. (1) First 10 c.c.; (12) twelfth 10 c.c. June 6th, 1903.
- After 60 c.c. had been collected, 60 c.c. of 3 per cent. NaCO was injected.
- | | | | | | |
|----------------|---|---------|---|---|---|
| After 70 c.c. | " | 50 c.c. | " | " | " |
| After 110 c.c. | " | 30 c.c. | " | " | " |
- The alkalinity of pilocarpin juice was not always so low. In one case it was equivalent to $\frac{N}{10}$ NaOH.

It will be noted that the juice obtained by injection of pilocarpin is much more concentrated than that produced after the injection of secretin. The gland seems to undergo exhaustion much more rapidly under the action of pilocarpin than under the normal stimulus of secretin. In whatever way it may be obtained pancreatic juice contains a number of ferments acting on the chief classes of food-stuffs. Thus, starch is rapidly converted by the juice into dextrine and maltose, and, if the juice be neutralised, the maltose is further converted into dextrose. The neutral fats are split up into fatty acids and glycerine. On proteins, juice obtained from a temporary fistula has very slight action. Boiled white of egg or gelatin are not digested even after weeks of soaking in the fluid. Fresh fibrin and caseinogen are slowly digested. The juice may therefore be said to contain a weak proteolytic ferment, resembling that which can be extracted from almost any tissue of the body. A similar ferment can be obtained from extracts of the intestinal mucous membrane, and has been named by Cohnheim *erepsin*. Its chief function in this situation appears to be the further digestion of albumoses and peptones, and their conversion into amino-acids. It seems, therefore, that the pancreatic cells, produced as an outgrowth from the mucous membrane of the intestine, have retained the power of producing this weak proteolytic ferment. These properties of fresh pancreatic juice were described by Claude Bernard, who regarded the proteolytic functions of the juice as unimportant. Corvisart, however, working, not with the juice as obtained from a cannula in the pancreatic duct, but with the juice as secreted

into the duodenum, described as one of its essential properties an extremely energetic action on proteins. Most of the later researchers dealt chiefly with an extract of the pancreas itself. All of these physiologists, of whom Kühne, Heidenhain and Langley may be specially mentioned, found that the watery extract contained not only lipase and amylase, but also a substance which rapidly underwent conversion into an active proteolytic ferment. The latter was named trypsin, and its precursor in the gland trypsinogen. In the juice obtained from permanent fistulæ, Pawlow found trypsin preformed, but showed later that part, at any rate, of the trypsin was present, not in the form of ferment, but as its precursor trypsinogen. Chepownikow, working in Pawlow's laboratory, found that the proteolytic activity of the juice was enormously increased by adding to it a drop of intestinal juice or of an extract of intestinal mucous membrane. He therefore concluded that the juice generally contained trypsinogen, which, under the influence of a ferment *enterokinase*, contained in the succus entericus, was transformed into the active ferment trypsin. Now it must be remembered that the juice obtained by Pawlow's method, before it is collected, has to trickle over the small portion of intestinal mucous membrane which is left in the abdominal wall surrounding the orifice of the duct. This mucous membrane can serve as a source of enterokinase, and Delezenne has found that if a cannula be inserted through the papilla into the duct, so as to prevent the juice coming in contact with the intestinal mucous membrane, the liquid so obtained contains no trypsin at all, and is without effect on coagulated protein. We may say, therefore, that juice, as it is secreted normally by the pancreas, contains no trypsin, but a precursor of trypsin named trypsinogen. We shall have to deal with the mechanism of this conversion in a later section, as also the influence of bile on the other fermentative actions of the pancreatic juice.

It is well known that most individuals possess the power of adapting themselves and maintaining health under very wide variations of diet. A man may satisfy his energy needs at the

expense of proteins, fats or carbohydrates. For perfect health all three constituents must be present in a diet, but their relative proportions may be varied within wide limits without causing any disturbance of the economy. Pawlow sought to explain this adaptation by a specific sensibility of the mucous membrane of the duodenum. According to researches carried out by Walther, a pupil of Pawlow, the composition of the pancreatic juice, and especially its contents in ferments, differed according as the animal were fed specially on proteins, fats or carbohydrates, the proper ferment predominating in each case. At the time that these researches were carried out, the part played by enterokinase in the activation of trypsinogen was not understood, and the experiments on the proteolytic powers of the juice are therefore worthless. In repetition of some of these experiments I have failed to find any constant proportionality between the amount of the protein ingested and the richness of the juice in trypsinogen, and Popielski states definitely that the relative amounts of the different ferments in the juice are not altered by altering the nature of the diet. A convenient opportunity for studying this question seemed to be offered by the observation of Weinland that normal pancreatic juice contains no lactase (the ferment converting lactose into grape sugar and galactose), whereas if taken from milk-fed animals lactase was present. Here, then, there was apparently a formation of lactase in the gland as a result of feeding with the food-stuff on which this ferment should act. This matter was re-investigated in my laboratory. At first results were obtained confirmative of Weinland's statement. The application of the improved method of analysis of Plimmer showed, however, that the results of previous observers were due to errors of analysis, and that the ferment lactase is never present in pancreatic juice, whether the animal be fed on milk or not. In this respect, therefore, it is certain that the pancreas has no power of adaptation. We have already seen that the normal activity of the pancreas is evoked, not by nervous changes, but by the production of a chemical messenger or hormone, which I have

called secretin. There is no evidence that, in the absence of this mechanism, stimulation of the mucous membrane of the intestine can cause any pancreatic secretion, and it is therefore still more improbable that a qualitative adaptation of the juice to the type of food-stuff is determined by such a nervous mechanism. There are riddles enough in physiology without conjuring up teleological adaptation for which the experimental evidence is inadequate, the conception of its mechanism impossible, and which is not necessary for the well-being of the animal.

Changes in the Pancreas during Secretion.—The normal pancreas consists of a series of secretory tubules which branch out from small ducts, the latter leading into a few large ducts. The small ducts are lined with a layer of narrow hyaline cells, the protoplasm of which does not stain with either basic or acid dyes. At the point where a duct becomes continuous with a secreting tubule, we find outside these hyaline cells a layer of typical secreting cells. In cross section, therefore, such an alveolus shows two layers of cells, the continuation of the duct cells in the centre being known as the centro-acinar cells. Towards the end of the alveoli the centro-acinar cells disappear, leaving only the secreting cells. The latter in an ordinary resting gland—i.e., one taken from an animal which has not had food for twelve to twenty-four hours—shows two well-marked zones. The outer zone consists of protoplasm with a strong affinity for basic dyes, such as hæmatoxylin or toluidine blue. The inner zone—i.e., that turned towards the lumen—is made up of a mass of coarse granules, closely packed together, which stain intensely with acid dyes such as eosine. The nucleus, which is round, and contains one or two well-marked acidophile nucleoli, is situated in the inner part of the protoplasm or basophile zone. If the gland has been secreting, the lumen of the alveoli contains a structureless material which, like the granules, stains deeply with eosine. If we study the process of activity in the living gland of the rabbit, as was done by Kühne and Sheridan Lea, we find that secretion, such as is produced by the injection

of pilocarpin, causes a diminution in the size of the cells and a discharge of the granules of the inner zone. We may conclude that here, as in the salivary glands, the act of secretion involves some change in the granules and their discharge from the cell in the form of secretion. In the pancreas, as in the submaxillary gland, the process of assimilation—i.e., the building up of fresh protoplasm from the surrounding lymph—and that of dissimilation—i.e., its continuous conversion into secretory granules—may go on simultaneously. It is evident that the occurrence of changes, such as I have described as the result of secretion, signifies a preponderance of the processes of dissimilation over those of assimilation, so that the whole cell gets smaller. This preponderance, however, is not a necessary feature of secretion. In the heart, for instance, the dissimilation which accompanies contraction is followed immediately or attended by an assimilation, which exactly balances the opposite process, so that the heart can continue to contract throughout the whole of natural life. The same balancing of two processes may sometimes be observed in the pancreas. Thus, in some cases we may excite a copious flow of pancreatic juice by the injection of secretin. Provided that the preparation of secretin is free from any large amount of the depressor substances, with which it is usually contaminated, the injection may be repeated time after time without interfering in any way with the general condition of the animal. In such an animal, with a good blood-pressure, a secretion may be produced continuously for as long as ten hours, and the pancreas at the end of this time may react as well to the injections as it did at the beginning of the experiment. If the animal be killed at the end of the experiment, the pancreas to the naked eye has the typical appearance of a resting gland. It is firm, opaque and whitish. On microscopic examination the cells are found to possess the two zones which are distinctive of a resting gland. In this case one must conclude that the injection of this specific stimulating substance, secretin, has excited not only dissimilation, but also assimilation, that it has, in fact, stirred up the total activities of

the living cells, so that there is a copious secretion without any loss of substance to the cells themselves. Usually the effect of repeated injections of secretin is to cause a gradual poisoning of the animal by the depressor substances, which are nearly always present in the decoction of intestinal mucous membrane, and the consequent diminution of the circulation interferes with the process of assimilation more than with that of activity or dissimulation. A similar interference can be brought about artificially if the animal be bled while the injections of secretin are being administered. In such an experiment the amount of secretion produced by each injection becomes less and less, until finally the gland ceases to respond at all. If the animal be now killed, the gland presents a greyish pink appearance, and is translucent and flabby. Sections made of such a gland, and stained with toluidine blue and eosine, show a diminution in the size of the cells and a diminution or entire disappearance of the red-staining granular zone.

The disappearance of the granules in the cells of the pancreas as the result of secretion excited by the injection of secretin is well shown in the preparations which accompany this memoir.* A study of these preparations brings to light certain other important factors relating to certain structures in the pancreas which have long engaged the attention of histologists and pathologists. In a normal section of a resting pancreas we may see scattered over the section collections of cells known as the "islets of Langerhans." These are small bodies varying in size, but generally of a diameter corresponding to between one and three secreting alveoli. They are composed of epithelial cells, free from granules, and taking all stains badly. Their nuclei are fainter than those of the adjacent tissue, and the cells are apt to shrink considerably in hardening fluids, indicating that in the living condition they were more or less dropsical. The blood capillaries between these cells are dilated and relatively more numerous than in the surrounding tissue, so that in an

* These preparations were produced in the Prize Essay, but not included in these Reports.

injected specimen of the gland it is easy to pick out the islets with the naked eye or by means of a hand lens. They have generally been regarded as composed of a tissue *sui generis*, and many pathologists have ascribed to them a function in the carbohydrate metabolism of the body. The evidence for this connection is, however, but slight. We know that ligature of the pancreatic ducts, although affecting digestion, does not cause glycosuria, whilst extirpation of the whole organ is invariably followed by fatal diabetes. Since the secreting acini of the gland have as their known function the formation of the pancreatic juice, the unexplained function of the gland, namely, the prevention of diabetes, has been connected with the unexplained structural element, namely, the islets of Langerhans. It has been stated that ligature of the pancreatic ducts causes degeneration of the secreting tissue, but leaves the islets intact. Opie and others have described changes, *e.g.*, hyaline degeneration in the islets, in cases of diabetes in man.

A study of sections of the pancreas which have been perfectly exhausted by repeated injections of secretin until no more secretion could be invoked, shows that during the functional activity of this gland there is actually production of islets of Langerhans. Even after moderate activity these islets are more numerous than in a resting gland, and in complete exhaustion almost the whole of the gland may be transformed into a tissue indistinguishable from that characteristic of the islets. In the resting gland cell we may distinguish beside the nucleus a basophile substance and the closely-packed mass of acidophile granules. Ordinary activity gives rise to a discharge of these granules, so that the cells, when stained with toluidine blue, have a prevailing blue colour. According to most histologists, this blue basophile substance is converted into the acidophile secretory granules. In complete exhaustion this basophile substance also disappears. The cell shrinks and becomes more watery. The arrangement into definite secretory tubules is disordered, so that the whole tissue has the appearance of that which is regarded as distinctive of the islets of Langerhans.

In many cases we can see an islet actively growing by a disappearance of the granules and basophile substances from the cells of the adjacent alveoli. Some of the large islets found in an exhausted gland may present in their middle tissue having the appearance of a normal secreting alveolus in which the discharge of granules and basophile substance is not yet complete.

I have made certain experiments to test the statement as to the effects of ligature of the pancreatic ducts on the islets of Langerhans. This procedure, whether carried out in the dog or rabbit, leads to a gradual atrophy of the secreting alveoli, more rapid in the latter than in the former animal. The granules and basophile substance gradually disappear, the alveoli shrink, and finally form masses of hyaline cells indistinguishable from islets. It is not true, however, that this process of degeneration leaves the islets unaffected. These also gradually disappear, so that there is a shrinkage of the whole gland. Even after a year, however, the atrophy of the gland is not complete, and it is therefore not surprising that this procedure does not bring about a condition of diabetes or glycosuria. We are therefore not justified in regarding the islets as a specific tissue with a function different from that of the secreting alveoli. These islets represent merely a phase in the normal life of the secreting alveoli. Sections of the foetal pancreas show that practically all the tissue of the gland is in what we may call the "islet condition," and indeed so long as active proliferation is going on, the secretory functions and the associated formation of basophile substances and granules seem to be in abeyance. We may regard the islets, therefore, as produced by a total exhaustion of the gland tissue. Whether in the adult animal they are destined to undergo complete disappearance, or whether they will by proliferation form new secretory alveoli, my evidence does not yet allow me to decide. The fact, however, that I have on one or two occasions found karyokinetic figures in the new islets formed under the influence of repeated injections of secretin incline me to believe that they are really destined to form new secretory alveoli.

An interesting fact was observed by Dale in my laboratory as to the influence of starvation on the structure of the gland. He found that the proportion of islet tissue to secreting tissue is increased not only by prolonged activity, but also by the prolonged inactivity which occurs during starvation. In the latter case the gland, which is not required for digestion, is called upon to give up its stored material, whether granules or basophile protoplasm, to serve as food for the organs on those parts of the body whose continuous activity is a condition of the maintenance of life, such as the central nervous system, the heart, and the respiratory muscles. In this process of wasting, the same changes are brought about in the appearance of the cells as when the discharge of their constituents is required for the production of a juice for the purpose of digestion.

Whether the pancreatic tissue in its islet stage has special connections with the carbohydrate metabolism of the body, or whether the antidiabetic functions of the gland are carried out by its alveolar cells in addition to and at the same time as their ordinary secreting functions, we are not yet in a position to state. Minkowski has shown that if a small fragment of the gland be transplanted under the skin of the abdomen, the remainder of the gland may be extirpated without causing diabetes. He has drawn attention to the fact that for this experiment to be successful it is necessary that the duct of the transplanted portion of gland should open on the surface. If by obstruction of this duct the secretory activity of the cells are impaired and degeneration brought about in the fragment of pancreatic tissue, diabetes invariably ensues. It seems, therefore, that the antidiabetic functions of the gland are more or less bound up with its secretory functions. Injection of extracts of the gland does not diminish in any way the diabetes caused by its extirpation, and we can, therefore, only assume that some substance is produced in the gland cells as a by-product in the exercise of their normal secretory functions, and it is this by-product which, after absorption into the lymph or blood stream, travels as a hormone to the various tissues of the body to

facilitate the assimilation or oxidation of the carbohydrates of the food.

(b) *The Secretion of Bile.*—In the case of the bile we are dealing with a fluid which is at the same time an excretion and a secretion. As the vehicle by which the products of disintegration of hæmoglobin are got rid of from the body, we should necessarily expect it to be formed constantly. So far as we know, the bile pigments which are derived from hæmoglobin play no further useful part in the body. They pass into the intestines and are excreted with the fæces in a more or less altered form as stercobilin. A small proportion is absorbed, passes into the blood stream and is excreted as the pigments of urine, namely, urochrome and urobilin, the latter of which is identical with stercobilin.

The other constituents of the bile, namely, the bile salts, lecithin and cholesterin, play an important part in the processes of digestion. Not only do they aid the action of pancreatic ferments, especially on carbohydrates and fats, but their presence in the gut seems to be a necessary condition of fat absorption. These substances are therefore required in the intestine while digestion is going on.

The continuity of excretion and the discontinuous passage into the gut is secured in most of the higher vertebrates by the provision of a reservoir, the gall-bladder in the course of the duct of the liver. In this receptacle the bile, which is being continuously secreted by the liver, accumulates between meals, and is only discharged therefrom into the intestine after the taking of food and its passage into the duodenum. During its stay in the gall-bladder the bile undergoes considerable concentration. There is an absorption of water, and the bile becomes slimy from the addition to it of mucin or, in some animals, nucleo-albumin, derived from the walls of the gall-bladder itself. The changes undergone by the bile in the gall-bladder are shown by a comparison of the composition of the bile from a biliary fistula with that from the gall-bladder.

ANALYSIS OF BILE. (Human.)

From a biliary fistula (Yeo and Herroun).		From the gall-bladder (Hoppe-Seyler) in 100 parts.	
Mucin and pigments	0.148	Mucin	1.29
Sodium taurococholate	0.055	Sodium taurococholate	0.87
Sodium glycocholate ...	0.165	Sodium glycocholate ...	3.03
Cholesterin	—	Soaps	1.39
Lecithin	0.038	Cholesterin	0.35
Fats	—	Lecithin	0.53
Inorganic salts ..	0.840	Fats	0.73
Water	98.7		

In order to determine the time relations of the secretion or of the excretion of bile into the gut, we must have recourse to fistulæ. These may be made in one or two ways. If we wish simply to determine the rate at which the bile is being formed by the liver we may ligature the common bile duct and establish a fistulous opening into the gall-bladder. The influence of various proceedings, such as the injection of bile salts or of secretin, on the rate of secretion of bile may be determined simply by placing a cannula in the hepatic duct. A method has been devised by Pawlow and used by other authors for determining the time relations of the flow of bile into the intestine. For this purpose the abdomen is opened and the common bile duct sought as it passes through the intestinal wall. The orifice of the duct with a piece of the surrounding membrane is cut out of the wall of the intestine, and the aperture thus made closed by sutures. The excised portion of mucous membrane with the opening of the duct is then sewn on to the surface of the duodenum, and the loop of duodenum at this point is stitched into the abdominal wound. After healing, the orifice of the bile duct is thus made to open on the surface of the abdomen.

In an animal treated in this way the flow of bile from the fistula is found to run parallel with the pancreatic secretion, though somewhat smaller in amount than the latter. Like the pancreatic juice, the flow of bile commences almost immediately

after taking food, attains its maximum with the pancreatic juice in the third hour, and then rapidly declines. It has been shown by Barbera that whereas the secretion of bile is greatest on a meat diet it is somewhat less on a diet of fat, and on a purely carbohydrate diet is practically insignificant.

In the flow of bile obtained under such circumstances two factors must be involved, namely—

- (1) Emptying of the gall-bladder;
- (2) The rate at which bile is being formed by the liver.

There can be no doubt that there is a reflex contraction of the gall-bladder as the acid chyme passes from the stomach into the duodenum. Experiments carried out in my laboratory show that the muscular wall of the gall-bladder is under the control of nerves derived both from the vagus and from the sympathetic (large splanchnic nerves). Stimulation of the vagus causes contraction of the gall-bladder, stimulation of the sympathetic, inhibition of the bladder. It is possible that these nerves are involved in a reflex initiated by the entrance of acid chyme into the duodenum. This reflex is not, however, easy to demonstrate in an anaesthetised animal. It is also possible that there may be a local nervous mechanism presiding over this reaction similar to that which, as we shall see later, is responsible for the movements of the intestines. Further investigations are necessary on this point. Information on the second factor, namely, the rate of formation of bile, is obtained from animals provided with a fistulous opening into the gall-bladder. In such animals we find, as we should expect, that the secretion of bile is continuous, but it is also evident that synchronously with the contraction of the gall-bladder, which occurs especially during the third hour after a meal, there is actually increased formation of bile by the liver. The entrance of acid chyme into the duodenum, therefore, stimulates the formation of bile by the liver just as it initiates the formation of pancreatic juice by the pancreas. The increased *secretion* of bile, which is produced by the passage of the acid chyme through the pylorus, can be also evoked by the introduction of acid, such as 0.4 per

cent. H.Cl., into the duodenum, and occurs even after division of all connection between the liver and the central nervous system. Since the presence of bile is necessary for the full development of the activities of the pancreatic juice, and its secretion is initiated by the same sort of stimulus, *i.e.*, acid applied to the mucous membrane of the gut, the question naturally arises whether the mechanism for the secretion of bile may not be identical with that for the secretion of pancreatic juice. In order to decide this point we must make a temporary biliary fistula by inserting a cannula into the hepatic duct. A solution of secretin is then prepared from an animal's intestine. In making this solution we must be careful to avoid any contamination by bile salts, which may possibly be adherent to the mucous membrane of the gut, and would in themselves, on injection, evoke an increased secretion of bile. It is therefore better to extract the pounded mucous membrane with boiling absolute alcohol until this fluid, evaporated to a small bulk, shows no trace of bile salts. The dried and powdered gut is then boiled with dilute acid. On injecting the solution of secretin so obtained into the animal's veins an increased flow of bile is at once produced. In one experiment, for instance, I found that the injection into the veins of 5 c.c. of a solution of secretin, prepared in this way, increased the secretion of bile by the liver from twenty-seven drops in fifteen minutes to fifty-four drops in fifteen minutes. The rate of secretion was therefore doubled. We must conclude from these experiments that the mechanism, by which the increased secretion of bile is produced at the time when this fluid is required in the intestine, is identical with that for the secretion of pancreatic juice, and that in each case one and the same substance—secretin—is formed by the action of the acid on the cells of the mucous membrane, and that this secretin, on absorption into the blood stream, excites both the liver and pancreas to increased activity.

The problem of the secretion of bile is not exhausted with the discovery of the stimulation action of secretin on the liver cells. If this were the sole mechanism involved we should

expect the secretion of bile to be always proportional to that of pancreatic juice. This is not strictly the case. It is true that the largest flow of both juices is obtained on a meat diet, but it is difficult to account for the fact that a carbohydrate diet excites a distinct flow of pancreatic juice while having practically no effect on the production of bile. It seems, therefore, that some other factor besides secretin is involved in the production of bile, and it is probable that this factor is the production of bile salts. At the present time we know nothing as to the conditions which determine the amount of bile salts formed in the liver. We know that the bile salts are absorbed from the intestine in order to be excreted in the bile, so that they are made to do duty in the intestine many times over. We know, moreover, that bile salts are the most effective cholagogues. I am inclined to believe that the action of food on the formation of bile takes place in two ways, namely—

- (1) By the formation of secretin in the walls of the gut;
- (2) By the direct stimulus given by the food *after absorption* to the manufacture of bile salts in the liver cells.

It may be that the products of protein digestion promote the formation of, or are directly converted into, bile salts, whereas carbohydrates may have no influence at all in this direction.

(c) *Succus Entericus*.—I have already mentioned that the addition of intestinal juice is necessary in order that the pancreatic juice may exert its strongly digestive action on proteins. In order to study its formation in the small intestine we may isolate loops of the gut by means of ligatures, and measure the amount of secretion formed in these loops in the course of a few hours' experiment on an anæsthetised animal. Better results may be obtained by establishing permanent fistulæ. In Thiry's original method a loop of intestine was cut out, and the continuity of the gut restored by suturing the two ends from which the loop had been severed. The open end of the loop was then closed, and the lower end sutured into the abdominal wound. Vella modified this method by leaving both ends of the loop open and suturing them into the abdo-

minal wound. This method has the advantage that it is easy to introduce substances into the upper end of the loop and determine the flow of juice from the lower end, the onward passage of the intestinal contents being provided for by the peristaltic contractions of the muscular intestinal wall.

I have established fistulæ by both these methods in a number of animals. Marked differences in the flow of juice are observed in such cases according as the fistula involves the upper or the lower portion of the small intestine. A condition which will cause a free flow of juice from a fistula high up in the intestine will generally cause a scanty flow from a fistula in the upper part of the ileum. In a dog with a fistula in the upper part of the jejunum the administration of a meal of meat provokes a flow of intestinal juice which may begin six to ten minutes after the meal. The amount of juice obtained remains very slight for about two hours, and then suddenly increases in amount during the third hour, thus corresponding to the flow of pancreatic juice and bile observed under similar conditions. As in the case of the pancreas, physiologists were formerly inclined to ascribe this post-prandial secretion of intestinal juice to nervous influence. The well-known experiment by Moreau in which denervation of an intestinal loop brought about a copious secretion of intestinal juice into the loop, was supposed to show the control of the central nervous system over the processes of secretion. I do not think that the cerebro-spinal system is involved in the ordinary secretion of succus entericus. It is certain that one may get a copious secretion of intestinal juice and, in fact, diarrhoea after extirpation of the nerve plexuses of the abdomen. Nor can we ascribe the post-prandial flow of juice to the co-operation of the local nervous system in the wall of the gut, though it is probable that this nervous system may take part in the secretory processes of the intestinal glands under certain conditions. In the animals with intestinal fistulæ all connection between the local nervous plexuses of the isolated loop and those of the rest of the alimentary canal have been severed in the primary operation.

We are driven, therefore, to the conclusion that the flow of intestinal juice which attends the passage of food into the first part of the duodenum must be excited by the formation of some chemical messenger. It seems probable that the chemical messenger by which the activity of the intestinal glands is aroused is identical with that which correlates the activity of the pancreas and liver with the entry of food into the duodenum. When collecting pancreatic juice by the intravenous injection of secretin I have always found the small intestine at the end of the experiment full, or containing considerable quantities, of intestinal juice. Delezenne and Trouin have shown that in animals provided with a permanent fistula of the duodenum or upper part of the jejunum, intravenous injection of secretin always causes a flow of intestinal juice. In the upper part of the gut, therefore, the simultaneous presence of the three juices necessary for complete digestion is ensured by one and the same mechanism.

Two other methods for chemically exciting the secretion of the intestinal glands have been described. According to Pawlow the most effective stimulus of the flow of succus entericus is the presence of pancreatic juice in the intestine. I have been unable to confirm this statement, but it is possible that the effect of the local introduction of pancreatic juice may vary with the location of the fistula. It is certain that the introduction of pancreatic juice into the blood stream does not arouse intestinal secretion, and I am inclined to believe that the effective stimulus in Pawlow's experiments was not any organic constituent of the juice, but the strongly alkaline character of this fluid. Introduction of alkalies or soaps into the gut always causes a profuse secretion of succus entericus. According to Trouin, a flow of intestinal juice can be excited by intravenous injection of the juice itself, even after boiling. If this be true it would seem that the flow of juice in the upper part of the gut, excited by the formation of (pancreatic) secretin, causes also the production of a different secretin or hormone in the intestinal juice itself. This hormone can be absorbed and

travel by the blood stream to lower segments of the gut, and thereby excite a secretion in preparation for the oncoming food. I have not yet made any experiments to test this point.

It is well known that the glands of the small intestine can be excited by direct mechanical stimulation of the mucous membrane. The easiest method of exciting a flow of intestinal juice from a permanent fistula is to introduce into the intestine a rubber tube. The presence of the solid object in the gut causes a secretion, and within a few minutes drops of juice can be obtained from the free end of the tube. The object of such a sensibility to mechanical stimuli is obvious; it is of the utmost importance that the onward passage of any solid object, especially if it be indigestible, shall be aided by the further secretion of juice in the portions of gut which are immediately stimulated. This mechanical stimulation probably acts on the tubular glands of the intestine through the intermediation of the local nervous system, the plexus of Meissner.

Properties of Succus Entericus.—Intestinal juice, as obtained from a fistula, is an alkaline fluid, generally turbid from the presence of leucocytes and desquamated epithelial cells. It contains about 1·5 per cent. total solids, including 0·8 per cent. inorganic salts (generally sodium chloride and sodium carbonate) The organic matter includes a number of ferments, which may be enumerated as follows:—

Enterokinase, which converts trypsinogen into trypsin;

Erepsin, which acts on proteoses and peptones, converting them into amino-acids;

Invertase, acting on cane sugar and transforming it into glucose and fructose;

Maltase, which converts maltose into glucose.

In all young mammals we find also *lactase*, which inverts milk-sugar, converting it into glucose and galactose. Various observers have also described a lipase, as well as a diastase, in the intestinal juice, but the presence of these ferments is inconstant. The seat of origin of these various ferments has been the subject of special investigation by Falloise. I have

already mentioned that secretin can be obtained from the whole thickness of the mucous membrane, and is probably therefore contained in the form of prosecretin in the epithelial cells covering the villi and lining the crypts of Lieberkühn. On the other hand, a superficial scraping of the mucous membrane, which removes only the epithelial cells covering the villi with the adherent mucus and intestinal secretion, gives a much more active solution of enterokinase than the deeper scraping of mucous membrane. This result is confirmed by Fallaise, who therefore places the seat of production of enterokinase in the cells covering the intestinal villi. The most active solutions of enterokinase are, however, to be obtained from the fluid found in the cavity of the intestine after the injection of secretin. I have therefore concluded that enterokinase is not present as such in the epithelial cells, but is first produced in the process of secretion and formation of the intestinal juice. The other ferments, namely, erepsin, maltase, invertase and lactase, probably pre-exist as such in the epithelial cells, especially in those lining the tubular glands of the gut, since pounded mucous membrane in water yields a solution of these ferments which is generally more powerful in its action than the succus entericus itself. So great is the difference, in fact, that many physiologists have suggested that the chief action of these ferments occurs, not in the lumen of the gut, but in the passages of the food-stuffs through the epithelial cells of the small intestine on their way to the blood vessels.

Mutual Interaction of the Duodenal Juices. The Interaction of Pancreatic Juice and Succus Entericus.—In an earlier section I have mentioned that pancreatic juice as secreted is only feebly proteolytic, and have ascribed this proteolytic power to the presence in the juice of a ferment similar to the erepsin which can be extracted from the intestinal mucous membrane. On coming into contact with a trace of intestinal juice, the pancreatic juice acquires a strong proteolytic activity. We may say that the juice as secreted contains a substance, trypsinogen, devoid of digestive power, whereas the juice after mixture with

succus entericus contains a strong proteolytic ferment, trypsin. Pawlow, in whose laboratory the activating influence of intestinal juice on pancreatic juice was first described, regarded the change as essentially of a ferment character. According to him intestinal juice contains a ferment, enterokinase, which has the property of transforming the trypsinogen of the pancreatic juice into trypsin. He therefore named enterokinase "the ferment of ferments." Delezenne, on the other hand, has sought to bring the interaction of these digestive juices into line with the phenomena studied by bacteriologists in the formation of antitoxins, hæmolysins, etc. According to Delezenne, enterokinase belongs to the class of cytases which have been described by Metchnikoff, and identified by him as products of the various types of phagocytes, especially the white blood corpuscles. These bodies are of almost universal occurrence, and are identical with those described by Buchner as alexins, and by Ehrlich as complements. These cell-dissolving substances cannot act on their object of attack without an intermediary substance which shall anchor them on to the substance in question. This intermediary substance, the immune body, or antibody, is specific, and varies with the substance to be attacked, e.g., red blood corpuscles. Metchnikoff and Delezenne regard the trypsinogen of the pancreatic juice as this intermediary body or amboceptor, which can lay hold of the protein molecule on the one hand, and of the cytase or enterokinase on the other, and so permit the latter to attack and break up the protein molecule. It is evident that these views are diametrically opposed to those of Pawlow. Delezenne has sought to support his view by the observation that the enterokinase can be abstracted from a fluid by means of fresh fibrin, just as the immune bodies can be abstracted from blood by red corpuscles in the cold, and be precipitated with them. The two views are, however, so fundamentally distinct that no difficulty is experienced in devising experiments which shall decide between the two. In the first place, according to Delezenne's view, there must be always a quantitative proportion between the amount

of enterokinase and the amount of trypsinogen; each "molecule" of enterokinase will need a "molecule" of trypsinogen to anchor it on to the protein molecule. The amount of enterokinase which may be added to a given solution of trypsinogen to impart the optimum proteolytic power to the solution will be reached directly the number of molecules of enterokinase equals that of the trypsinogen. This condition, once attained, will be permanent, and under no condition could we expect, by the use of a minimum quantity of enterokinase, to evoke a maximum proteolytic activity by allowing a longer time for the interaction to take place. On the other hand, this is precisely what would happen if the enterokinase acted as a ferment. A larger amount of enterokinase would convert the trypsinogen rapidly into trypsin, while the same effect should be produced by a much smaller amount of enterokinase if only interaction were allowed to go on for a much longer time.

I therefore instituted a number of experiments on the quantitative relationships of enterokinase to trypsinogen. Fresh pancreatic juice, with or without the addition of sodium fluoride, was treated with quantities of enterokinase varying from .0001 c.c. up to an equal bulk, and the action of the mixture at once tested on gelatin tubes and on coagulated egg white. It was found that if the experiment was allowed to go on for two days before interruption, the differences between the results were only slight, and that it was very difficult to determine any optimum point for the amount of enterokinase. On the other hand, if the observations of the tubes were made repeatedly at short intervals, it was found that at first there was a very marked difference in the activities of the various mixtures, those containing a large amount of enterokinase being very active, while those containing the smallest quantities might be absolutely inactive. Later on these differences gradually disappeared. There was a rapid increase in the proteolytic activity of the solutions containing the traces of enterokinase, while, at room temperature, those containing larger amounts slowly diminished in activity. These experiments, therefore, confirmed Pawlow's

view, the enterokinase resembling in its action a ferment, and acting directly on the trypsinogen rather than in co-operation with it. If Delezenne's view were correct, every known trypsin must owe its activity to the existence in it of the two bodies trypsinogen and enterokinase. If, therefore, we can by any means exclude the presence of enterokinase from such a solution we can be certain that its activity must be due, not to trypsinogen, but to a third substance, namely, trypsin. The distinguishing character of enterokinase, in fact the only character by which we can judge of its presence, is its power of activating pancreatic juice. If the trypsin solutions contain enterokinase, they also must possess the power of activating pancreatic juice. A series of experiments devoted to the decision of this point has shown that the proteolytic power of the pancreatic juice, *plus* trypsin is less than that of sodium carbonate containing the same strength of trypsin. There is no doubt that Grubler's trypsin has no activating power on pancreatic juice, and, therefore, contains no enterokinase. It may indeed digest and destroy trypsinogen without activating it. The hydrolytic splitting of trypsinogen, that is to say, does not necessarily involve its conversion into trypsin.

Another method has given identical results. If enterokinase be injected several times into the blood stream of an animal over a period of two weeks, the serum of the animal acquires the property of destroying this ferment owing to the development in it of antikinase. If trypsin were a mixture of trypsinogen and enterokinase, anti-trypsin should also have an anti-kinasic power. I have found that it is possible to obtain a serum which has only slight anti-tryptic power, but strong anti-kinasic power, or one which has a strong anti-tryptic power, but has no power of hydrolysing enterokinase.

Moreover, I have not been able to confirm Delezenne's observations on the affinity of fibrin for enterokinase. Flakes of fibrin were soaked in enterokinase solutions for a considerable time, but no diminution occurred in the amount of enterokinase contained in the fluid. The fibrin certainly took up a small

trace of enterokinase, and was therefore able to activate pancreatic juice, but it would take up any other ferments in the same way, and this fact does not indicate any specific attraction of the fibrin for enterokinase. We must therefore conclude that enterokinase is a ferment with a specific action on trypsinogen. When it has effected a conversion of trypsinogen into trypsin its office is finished, and it takes no further part in the action of trypsin on the protein constituents of the food. It is, in fact, rapidly destroyed at the temperature of the body, especially in the presence of trypsin or in an alkaline fluid.

What is the nature of this action? If, as in the case of so many other ferments, it is merely a hydrolysis, we should expect to be able to imitate its effect by chemical means, and many physiologists have described various methods of activating pancreatic extracts, *i.e.*, of converting trypsinogen into trypsin, by simple chemical means such as the addition of weak acids, oxygenation, etc.

According to Delezenne, various additions, especially of leucocytes and lymph corpuscles, can effect the activation of trypsinogen, and many observers have described a slow spontaneous activation of the juice after its secretion. In my earlier experiments I was unable to obtain activation by any means other than the addition of enterokinase, and therefore ascribed the so-called spontaneous activation of pancreatic juice to accidental contamination with small traces of enterokinase. At that time I worked chiefly with pancreatic juice to which about 1 per cent. sodium fluoride had been added as an antiseptic. Since the addition of this salt does not interfere with the activation of the juice by enterokinase, or with the digestive action of trypsin, I regarded it as an indifferent substance, so far as the juice was concerned. Sodium fluoride, however, precipitates all soluble calcium salts, and in the light of more recent researches we must conclude that many of the statements which I have made and published apply only to a juice freed in this manner from lime salts. In 1905 Delezenne stated that pancreatic juice could be activated by the addition to it of lime salts, *e.g.*,

calcium chloride, and certain other salts, such as those of magnesium or barium. These results were confirmed by Zuntz, who carried out a comparative study of the relative activating effects of the various metals without, however, adding materially to the results obtained by Delezenne. According to the latter author the activation takes place suddenly, as a rule after from twelve to fifteen hours in the incubator, but the activation may be more rapid if the optimum amount of calcium salt be added. The activated juice can be freed from the calcium salt by dialysis or by the addition of sodium fluoride or ammonium oxalate without losing its activity. Delezenne does not consider the action of calcium salts comparable to that of enterokinase, nor does he find these salts necessary to the action of enterokinase, since this ferment activates pancreatic juice in the presence of excess of sodium fluoride, as I have already shown. He suggests that the calcium takes part in the formation of enterokinase from a precursor, *prokinase*, in a manner analogous to that in which calcium determines the formation of fibrin ferment from its precursors, thrombokinae and thrombogen.

A repetition of these experiments has resulted in confirming the power of calcium salts to activate pancreatic juice. I have not yet succeeded, however, in thoroughly clearing up the nature of its action. It is interesting to note that although the addition of calcium salts to fresh pancreatic juice causes the conversion of trypsinogen into trypsin, it is not possible, by the addition of any quantity of calcium salts to juice, *previously* decalcified by the addition of sodium fluoride, to effect any activation, nor have I been able to find any evidence in favour of the view advanced by Delezenne that the calcium salts cause a conversion of a prokinase present in the juice into enterokinase. Pancreatic juice which has been activated by calcium salts has no further activating power on fresh quantities of juice, *i.e.*, it does not contain enterokinase. The spontaneous activation of pancreatic juice, as well as the slow activation which may ensue on the addition of lymph corpuscles, etc., are really due to the presence of calcium salts, and do not occur after decalcifi-

cation of the juice. The calcium activation seems, in fact, to be quite independent of the activation by enterokinase. It is not probable, however, that the activation by calcium plays any part in the normal processes of digestion. It is incomparably slower than the process of activation by enterokinase, and has probably only a theoretical importance. The absolute identity of the final results of the action of an inorganic salt and of a ferment has, so far as I know, no analogies in the case of other ferments, and the curious relation between these phenomena and the temperature at which they are effected is at present difficult to understand. Further research along these lines should materially advance our knowledge of the intimate nature of ferment action.

The Interaction of Bile and Pancreatic Juice.—Although itself containing no ferments, bile exerts an important adjuvant action on the other juices, especially pancreatic juice. It is true that a weak amyolytic ferment has been described in bile, but the value of the bile depends not on the presence of this ferment, but on the peculiar action of the bile salts, an action which is bound up with their other physical properties. It was shown long ago by Williams and Martin that the amyolytic power of pancreatic extracts is doubled by the addition of bile or bile salts. Pawlow has stated that the same holds good of the proteolytic power of this juice. Most important, however, is the part played by the bile in the digestion and absorption of fats. The fat-splitting action of pancreatic juice is trebled by the addition of bile, whether boiled or unboiled. This quickening action of the bile probably depends, like its function in the absorption of fats, on the peculiar physical properties of the bile salts with those of the lecithin and cholesterin, which are held in solution. Not only does such a solution diminish the surface tension between watery and oily fluids, so promoting the closer approach by the lipase of the pancreatic juice to the fats on which it is to act, but it has also the power of dissolving fatty acids and soaps, including even the insoluble calcium and magnesium soaps. It is probable that it aids also in holding

in solution, and bringing in contact with the fat, the lipase of the pancreatic juice. It has been shown by Nicloux that the lipase contained in oily seeds, such as those of the castor plant, is insoluble in water, but soluble in fatty media. The dried ferment obtained from the pancreas in many cases yields no lipase to water, but gives a strongly lipolytic solution when extracted with glycerin. The digestive function of bile, therefore, lies in its power of serving as a vehicle for the suspension and solution of the interacting fats, fatty acids, and fat-splitting ferment. This vehicular function plays an important part in the absorption of fats. These pass through a striated basilar membrane bounding the intestinal side of the epithelium, not, as has been formerly thought, in a fine state of suspension (an emulsion), but dissolved in the bile in the form of fatty acids or soaps and glycerin. On the arrival of these products of digestion in the epithelial cells, a process of resynthesis is set up. Droplets of neutral fat make their appearance in the cells, whence they are passed gradually into the central lacteal villus, and so into the lymphatics of the mesentery and into the thoracic duct. The bile salts, thus released from their function as carriers, are absorbed by the blood circulating through the capillaries of the villi, and carried by the portal vein to the liver. Arrived here they are at once taken up by the liver cells and turned out into the bile. Owing to the fact of their ready excretion by the liver cells, bile salts are the most reliable cholalogues with which we are acquainted. By this circulation of bile between liver and intestine, the synthetic work of the liver in the production of the bile salts is reduced to a minimum, and it has only to replace such of the bile salts as undergo destruction in the alimentary canal, under the influence of micro-organisms, and are lost to the organism by passing out in the fæces as a gummy amorphous substance known as dyslysin.

3. Changes undergone by the Food in the Small Intestine.—

We have seen that the contents of the stomach begin to be discharged from the pyloric orifice within five to twenty minutes

of the time at which the meal is taken, and that this discharge is continued at repeated intervals for the next four hours, the most rapid discharge occurring in the third hour. The chyme entering the duodenum is strongly acid in character from the presence of hydrochloric acid. It contains a small portion of undigested food-stuffs, the greater portion having been already brought into a state of solution. The chyme, therefore, contains acid albumin, proteoses and peptones, dextrin, sugar and starch, neutral fat which has been set free by the solution of the protoplasmic envelopes of the fat cells, and a certain amount of fatty acids resulting from the lipolysis which has occurred in the stomach.

The pylorus is provided with a local reflex mechanism which automatically prevents the duodenum being flooded at any one time with a large quantity of the acid chyme. The pylorus opens when the chyme, which arrives at its gastric side, has a certain degree of acidity. Directly this acid chyme arrives in the duodenum the pylorus is shut, and remains closed so long as the contents of the upper part of the duodenum remain acid. But the entrance of acid chyme into the duodenum initiates the whole chain of adapted processes which result in the neutralisation of the chyme, and thus allow the pylorus to open again and admit a further small quantity of the gastric contents into the duodenum. The contact of the acid with the duodenal mucous membrane brings about the formation in the intestinal epithelial cells of secretin. This secretin is not turned out into the intestine. I have shown that secretin is either not absorbed by the introduction of secretin into the lumen of the gut. the intestinal wall. It is impossible to evoke pancreatic secretion by the introduction of secretin into the lumen of the gut. The secretin, however, which is formed within the epithelial cells passes directly into the blood vessels of the intestinal villi, and is carried by the blood through the heart and lungs and the systemic circulation to the pancreas. On its way it also passes through the liver, and it is also able to influence the glands of Lieberkühn with which the internal wall of the

intestine is closely beset. As a result, we obtain simultaneous secretion of the three juices, namely, pancreatic juice, bile, and succus entericus. Two of these, namely, pancreatic juice and succus entericus, are alkaline. Bile, which is practically neutral, has the property of precipitating certain of the albumoses, as well as acid albumin. The formation of secretin and the secretion of alkaline juices will proceed until the contents of the upper part of the small intestine are exactly neutralised. The secretion will then stop, but the neutralisation of the duodenal contents allows the pylorus to open once again and to admit a further quantity of acid chyme, so that the same march of events is instituted as before. We see, therefore, that all these mechanisms are arranged so as to ensure a practical neutralisation of the contents of the upper part of the small intestine, and it is in this neutral medium that the main digestive processes of the intestine take place. I have already indicated the main character of these processes. By means of the trypsin formed by the action of enterokinase on the trypsinogen of the pancreatic juice, the primary products of proteolysis formed in the stomach, namely, albumoses and peptones, are converted into amino-acids. A small residue of the proteins resists complete disintegration and is found in the intestinal contents as a polypeptid, from which, by acid hydrolysis, alanine, glycine, and phenyl alanine may be obtained. Proteins which have resisted gastric digestion are rapidly dissolved by the trypsin and carried through the stages of secondary proteose and peptone into amino-acids. In the further disintegration of the proteoses and peptones the ferment erepsin of the succus entericus plays a part. The proteins are thus entirely broken up in the intestine into their constituent amino-acids, and it is probably in this form that the greater part of them are absorbed by the wall of the intestine. As we have seen, at the lower end of the small intestine not only is digestion complete, but nearly the whole of the products of digestion have been taken up by the intestinal wall.

The fats which enter the duodenum, generally as neutral fats, but partly as glycerin and fatty acids, undergo rapid hydrolysis under the combined action of the bile and the pancreatic juice. The lipase contained in the latter splits up the fats into fatty acids and glycerin. The fatty acids are dissolved in the bile and carried as such into the intestinal wall. If these acids come into contact with the alkaline intestinal juice, they will combine with the alkalies to form soaps. The soaps, however, are equally readily dissolved by the bile, and after absorption are converted in the epithelial cells into neutral fats by recombination with glycerin.

The carbohydrates are entirely converted into monosaccharides, chiefly glucose. The four assimilable hexoses are mannose, glucose, fructose and galactose. The first of these does not play any important part in the normal dietary. Under the influence of the pancreatic juice, starch is converted to maltose by the diastase present, and this is further converted into glucose by the maltase. Maltase is also present in the succus entericus. The two other chief sugars which are found in a normal diet, namely, cane-sugar and milk-sugar, are reduced to monosaccharides by the action of the ferments contained in the succus entericus and also in the epithelial cells lining the gut. Cane-sugar yields under the influence of invertase, glucose and fructose. Milk-sugar is converted by the lactase of the intestinal wall into glucose and galactose. We see, therefore, that the stomach acts as a reservoir and prepares the food so that it may be admitted in small quantities and semi-digested into the more delicate structures of the small intestine. In the latter organ the processes of digestion are completed and carried to their end stages. As digestion is proceeding, absorption is also going on, so that at no time in the small intestine is there any considerable accumulation of the products of digestion. In this way we have in the small intestine ideal conditions for the ferments of the digestive juices to effect their work in the smallest time. Not only do the ferments destroy the food-stuffs, but they themselves end by being

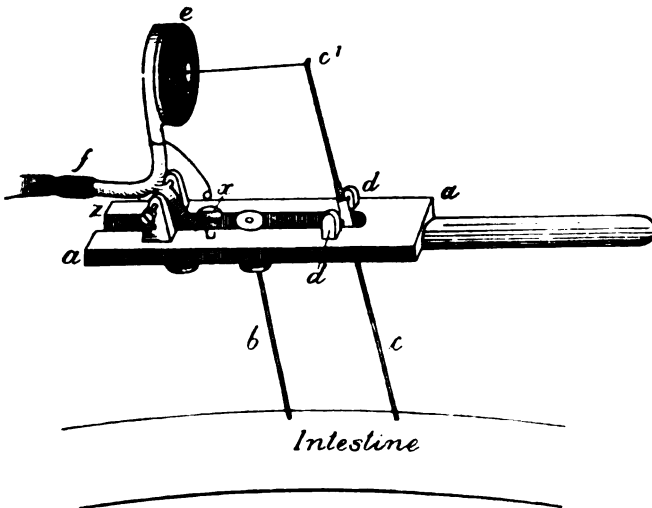
destroyed. An infusion of the intestinal contents from the lower end of the ileum is found to contain practically no trypsin and only slight traces of the other intestinal ferments, such as diastase, lipase, erepsin and enterokinase. The process of digestion and absorption is therefore practically complete by the time that the food has arrived at the ileo-cæcal valve.

4. *Movements of the Small Intestine.*—Until ten years ago there was no subject in physiology where we met with so many discrepancies, both of fact and of opinion, as in that of the physiology of the intestinal movements. These discrepancies are due to the fact that earlier observers failed to exclude in their experiments the many disturbing impulses which can play on any segment of the gut, either reflexly from the central nervous system or from other parts of the alimentary canal itself through the local nervous system. Moreover, I have found that the motor mechanism of the intestinal wall is extremely sensitive to changes in the blood flow through the vessels of the gut and to the presence of drugs or other chemical substances in the blood or within the gut itself.

The movements of the intestine may be observed either in the intact animal or after exposure of the intestines in the anaesthetised animal. In the former case the movements are rendered visible by the administration of large quantities of bismuth sub-nitrate with the food. This substance, being opaque to the Röntgen rays, enables the movements of the contents of the alimentary canal to be observed when the animal or man is placed in front of a fluorescent screen and Röntgen rays allowed to pass through the body. Valuable observations by this method have been carried out by Cannon in America and by Hertz in this country. The method has the advantage that no disturbing influences are present to interfere with the normal course of the intestinal movements. It does not, however, allow us to analyse these movements or to determine the muscular and nervous factors involved in their production. My work has been chiefly carried out on the exposed intestine in mammals. I will describe first the movements as studied in this way, and

later consider, in the light of Cannon's researches, the significance of the movements for the normal progress of the food in the gut.

In most of my experiments I have graphically recorded the movements of the muscular coats of the intestine. Contraction of the circular coat of the intestine will diminish the lumen, and in certain conditions of the gut may increase it in length. Contraction of the longitudinal coat will shorten the gut, and might, theoretically, cause a slight increase in its transverse diameter. The most convenient way of recording the contractions of the circular coat is to introduce into the lumen a capsule of fine rubber which is tied on to the end of a small metal tube about five inches in length. This may be inserted either through the cut end of a loop of intestine, which is then tied tightly round the tube, or, better, through a small longitudinal incision in the unattached margin of the intestine. After the insertion of the tube, the incision is closed by two stitches of fine thread, one of which is taken round the tube. The capsule is distended with air under a pressure of about 10 ccm. of water, the capsule being connected through a small water manometer to a piston recorder which registers the movements of the water column, and thus the contractions of the circular coat on the lever of the capsule. It is often useful to be able to register the contractions of the muscular wall without the introduction of any foreign substance into the gut. For this purpose I have devised an instrument, which I have called an enterograph, by means of which we may record the contractions of either the longitudinal or circular coat, or of both coats simultaneously. The construction of the enterograph will be evident from the diagram. The two needles B and C are tied by a thread to the outer wall of the intestine. B is fixed, and C can rotate round the axis DD. Approximation of C to B by contraction of the longitudinal coat of the intestine will cause a movement of the upper end of C outwards, and therefore will pull upon the membrane of the tambour E.



In discussing the physiology of the intestinal movements, it will be simpler to consider, in the first place, the behaviour of the gut which has been freed from all nervous connections with the central nervous system. This may be effected in various ways. In two experiments I divided both vagus nerves, cut through the cord just below the medulla, and then excised the spinal cord from the seventh cervical to about the fourth lumbar nerve. In two other experiments I excised the whole of the ganglionic mass surrounding the celiac axis and the superior mesenteric artery, clearing these vessels of all nerve-filaments; divided the mesentery; extirpated the abdominal sympathetic chain on each side, and cut both splanchnics and both vagi. Although these experiments are the only ones in which one can be absolutely certain of having destroyed all nervous connections between intestine and central nervous system, the results obtained differ very slightly, if at all, from those obtained after simple section of both splanchnic nerves alone or of both splanchnics and both vagi.

On opening the abdomen in a warm saline bath, it will be seen that the intestines are in a state of active movement. Two kinds of movement may generally be distinguished. The first

of these are the so-called pendulum movements ("Pendelbewegungen"), all the coils being affected by a gentle swaying motion, which has been generally ascribed to contractions of the longitudinal coat. On close observation these swaying movements are seen to be accompanied by very slight waves of constriction, which pass rapidly down the intestine. These waves may apparently originate at any part of the gut, but so far as I have been able to ascertain, pass almost exclusively from above downwards. The small extent of the movement and the varying origin of the waves make it difficult to estimate accurately their rate of transmission, which apparently varies from 2 to 5 cm. per second. Besides these slight contractions one will generally notice portions of the gut which are the seat of a strong contraction of the circular coat. This contraction obliterates the lumen both of the gut and of the blood vessels, so that the affected portion becomes blanched. This ring of constriction travels slowly down the gut, and corresponds exactly to the accepted idea of a peristaltic contraction. The rate of propagation of the wave decreases as the contraction increases in force, and may take as much as 10 seconds to travel 1 cm. On close observation, it will be seen that this wave is preceded by a wave of inhibition, the portion of the gut immediately below the constricted area being relaxed and motionless. In some cases two or three waves of constriction may be seen immediately following one another, each wave being separated from the adjoining one by a small length of reddened relaxed gut. In no case do these waves move upwards; that is to say, there is no antiperistalsis. They may traverse the whole length of the small intestine and be transmitted to the colon, or they may gradually diminish in force and die out in their course. If absent, they may be easily excited by electrical or, better, mechanical stimulation of any portion of the intestine. In order to study the causation of these movements we must employ graphic methods, and we may deal with each kind of movement separately.

Pendulum Movements.—On inserting the rubber capsule already described into the gut, and connecting it with a piston

recorder, it will be seen that the intestinal wall is the seat of continuous rhythmic contractions, which cause a diminution of the lumen and are synchronous with the pendulum movements as observed by the eye. Each contraction and relaxation lasts from 5 to 6 seconds, so that they are repeated at the rate of 10 or 12 per minute. In many cases the intestine beats with the regularity of the heart; in others the contractions are more or less irregular, varying in size or ceasing altogether for one or two beats. By means of the enterograph it is possible, without opening the gut, to record the movements of either circular or longitudinal muscular coats, and it is then found that both coats present rhythmic contractions at the same rate, the two coats at any point contracting synchronously. When the contractions are recorded by means of a balloon, the constriction which accompanies each contraction is seen to be most marked at the middle of the balloon, *i.e.*, at the point of greatest tension, and the amplitude of the contractions is augmented by increasing the tension on the walls of the gut. These movements are unaffected by the direct application of drugs, such as nicotine or cocaine, which we might expect to paralyse any local nervous structures in the wall of the gut. I therefore concluded that these rhythmic contractions were myogenic, that they were propagated from muscle fibre to muscle fibre, and that they coursed down the gut at the rate of about 5 cm. per second. Since, however, they may apparently arise at any portion of the gut which is subject to any special tension, it is not easy to be certain that a contraction recorded at any point is really propagated from a point two or three inches higher up. I suggested that the action of these contractions was to cause a thorough mixing of the contents of the gut with the digestive fluids.

Magnus has shown that it is possible to pull off strips of the longitudinal (outer) coat of muscle fibres from the small intestine. Such strips, if they contain Auerbach's plexus, will contract rhythmically if kept in warm oxygenated Ringer's fluid. If, however, the plexus has been left behind in stripping off the

muscle, no rhythmic contractions are to be observed, although contraction can still be excited by artificial stimulation. Magnus concludes that even the rhythmic "pendular" contractions depend for their occurrence on the integrity of the connection between local ganglionic centres and muscle fibres, and cannot therefore be strictly regarded as myogenic.

In order to determine the significance of these pendular movements in the normal processes of digestion we must have recourse to the method devised by Cannon. On examining under the Röntgen rays the intestines of a cat, which has taken a large meal of bread and milk mixed with bismuth some hours previously, a length of gut may be seen in which the food contents form a continuous column. Suddenly movements occur in this column, which is split into a number of equal segments. Within a few seconds each of these segments is halved, the corresponding halves of adjacent segments uniting. Again, contractions recur in the original positions, dividing the newly-formed segments of contents and reforming the segments in the same position as they had at first. If the contraction is a continuous propagated wave, it is evidently reinforced at regular intervals down the gut, so as to divide the column of food into a number of spherical or oval segments. In this way the points of greatest tension immediately become the points which are midway between the spots where the first contractions were most pronounced. The second contractions, therefore, start at these points of greatest tension, and divide the first-formed segments into two parts, which join with the corresponding halves of the neighbouring segments. In this way every particle of food is brought successively into intimate contact with the intestinal wall. These movements have not a translatory effect, and a column of food divided up in this way may remain at the same level in the gut for a considerable time.

Peristaltic Contractions.—Peristaltic contractions may occur spontaneously in the (nervously) isolated small intestine, or, if absent, may be evoked by local stimulation. For this purpose a mechanical stimulus, such as a pinch, is more effective than

electrical stimulation, even when this latter is applied to the inner surface of the intestine by means of specially formed electrodes. Extremely powerful peristalsis may be excited by injecting strong solutions of sodium chloride into the lumen of the gut by means of a hypodermic syringe. The most certain and the best, because the most physiological, method of exciting a peristaltic wave is to insert a bolus, which may be made of cotton-wool covered with vaseline, into the intestine. On isolating about a foot of intestine and inserting the bolus about one inch from the upper end, it will be seen that shortly after putting in the bolus the contractions of the segment of intestine immediately above it undergo increasing augmentation, until the intestine at this point enters into a strong tonic contraction. This presses the bolus onwards, and as it moves the ring of contraction follows it up until it has expelled the bolus through the lower opening of the coil. As the bolus passes down the intestine it will be noticed that the whole part of the gut above it is in a state of activity, waves of constriction passing down it as far as the constricting ring. In some cases, after the bolus has been expelled, a second slow peristaltic wave of contraction may pass from one end to the other as if to expel any detached portions of the bolus that may be left behind. The progression occurs only in one direction, from above downwards. This rule is so invariable that one may determine which is the upper end of an isolated two inches of gut by seeing in which direction a bolus is expelled. If the bolus be inserted from below and pushed up the gut it will be returned by the way it has entered. If, however, the intestine is in good condition, this latter experiment becomes impossible. As we attempt to push up the lump of cotton-wool, the intestinal wall contracts strongly above it, and resists the upward passage of the bolus to such an extent that we may tear the intestinal wall before we can push the bolus any further.

The conditions in the intestine which determine the movement of a bolus from above downwards will be better seen if we

record the contractions of the longitudinal and transverse coats at a point about the middle of a coil of intestine, through which a peristaltic wave of contraction is excited by the insertion of a bolus. Thus, in one experiment two enterographs were placed at right angles to one another at about 130 cms. from the pylorus. A bolus made of cotton-wool coated with vaseline was then inserted by an opening into the intestine $4\frac{1}{2}$ inches above the enterographs. Immediately on the introduction of the bolus the rhythmic contractions of the circular coat ceased instantly, and gave place to a gradually increasing relaxation. On inspecting the intestine it was seen that the introduction of the bolus caused the appearance of a strong constriction above it. This constriction passed downwards, driving the bolus in front of it, the onward passage being rendered easy by the complete inhibition of all the coats of the intestine below. Directly the bolus passed under the enterograph levers a strong contraction of both coats occurred, emptying the intestine at this point by pushing the bolus onwards down the intestine. The processes involved after this onward movement of the bolus, *i.e.*, in a true peristaltic contraction, are revealed if we investigate the propagated effects up and down the intestine of local stimulation. If a balloon be inserted in the lumen of the exposed gut, it will be found that pinching the gut *above* the balloon causes an immediate relaxation of the muscular wall in the neighbourhood of the balloon. This inhibitory influence of the local stimulus may extend as much as two feet down the intestine towards the ileo-cæcal valve. On the other hand, pinching the gut half an inch below the situation of the balloon causes a strong continued contraction to occur at the balloon itself. We see, therefore, that stimulation at any portion of the gut causes contraction above the point of stimulus and relaxation below the point of stimulus (the "law of the intestines"). The same effect is produced by introduction of a bolus of food, especially if it be large or have a direct irritating effect on the wall of the gut. In this case the contraction above and the inhibition below cause an onward movement of the bolus,

which travels slowly down the whole length of the gut until it passes through the ileo-cæcal opening into the large intestine.

It is evidently impossible to explain this complicated reaction of the isolated gut to local stimulation on any hypothesis which does not take into account the occurrence of a complicated system of nerve fibres and ganglion cells in the wall of the intestine. We cannot imagine any muscle fibre or collection of muscle fibres which would relax on one side and contract on the other side of an excited point. Nothnagel showed that the application of a crystal of a sodium salt to the wall of the gut in cats and rabbits produced a ring of constriction about 1 cm. higher up, whereas with potassium salts the constricted ring was at the point of application. He concluded that potassium salts excite the muscle fibres directly, while the action of sodium salts is chiefly on Auerbach's plexus. Apart from this observation, although many physiologists have invoked the aid of Auerbach's plexus to explain the propagation of the peristaltic wave, no proof has been furnished against Engelmann's contention that the whole process has its origin in and is carried out through the muscle fibres. The tendency of physiologists during the last thirty years has been to deny to peripheral ganglia, or collections of ganglia, any reflex functions at all comparable to those possessed by the brain and spinal cord--functions, that is to say, which include co-ordination as well as mere reflection of impulses. The facts here brought forward, however, show beyond doubt that the local nervous structures in the gut have this power of co-ordination, of directing one kind of influence along one path, and another kind of influence along another path, the result being a "purposive" response directed to the propulsion of the food down along the alimentary canal. Auerbach's plexus is, in fact, a local nervous system with two reflexes, inhibition and augmentation, and one function, propulsion of food. The different time relations of the two reflexes would lead one to suppose that the system is composed of long paths which conduct inhibitory impulses downwards, and short paths which carry augmentor impulses from one cell station

to another in an upward direction. A histological testing of this hypothesis presents, however, considerable difficulties.

It now becomes important to inquire how the motor functions of the intestine will be modified if we abolish or paralyse the action of its local nervous system. A temporary paralysis of this system, lasting from 10 to 40 minutes or more, may be produced in various ways. One method we have adopted is to paint the surface of an exposed coil of intestine with a $2\frac{1}{2}$ per cent. solution of cocaine in normal saline. The same effect can be produced by the injection of nicotine (2 to 3 c.c. of a 1 per cent. solution in a dog of 7 kilos.), or by the injection of large doses of muscarin (3 c.c. of a 0.1 per cent. solution). An intestine, the nervous system of which has been paralysed by one of these methods, at first sight presents very little difference from the normal. It appears, if anything, rather more active. The rhythmic contractions, which before may have been irregular, now become perfectly regular and often more powerful. They run as waves of constriction over the gut, but the waves pass as often in one direction as in the other. The following table represents a series of observations of rates of propagation of such waves :—

	Length of intestine.	Time of propagation.	Rate per sec.
1. Ascending wave . .	8 cm.	3.5 secs.	2.3 cm.
2. Ascending wave ...	15 "	6.0 "	2.5 "
3. Descending wave . .	7 "	3.25 "	2.2 "

It will be seen that the rate is somewhat slower than that of the similar waves in the normal intestine.

In the paralysed gut it is impossible, however, by stimulating above or below the recorded spot, to cause any alteration at all, either of inhibition or augmentation in the strength of the contractions. A slight pinch has no effect on the intestine. A very strong pinch causes a band of constriction in consequence of the direct stimulation of the muscle fibres. This constriction passes off gradually without being propagated in either direction.

A bolus may be placed anywhere within such an intestine without causing any change. The bolus remains in the spot where it was inserted.

These results show that I was justified in my distinction of two kinds of movements in the intestines. In the first place, we have the rhythmic pendular movements produced by simultaneous contractions of circular and longitudinal coats, and chiefly myogenic in origin. They are propagated from muscle fibre to muscle fibre, and travel in either direction along the intestines at a rate of 2 to 3 cm. a second. The preponderance of the descending contractions in the normal animal may be due to the higher excitability of the fibres at the duodenal end of the gut, and to the constant presence of ascending augmentor stimuli. They are independent of the intestinal nervous system for their production or propagation, although they can be altered in the direction of inhibition or augmentation through the intermediation of this system.

The peristaltic contraction, on the other hand, is a true co-ordinated reflex excited by the distension of the gut at some point, or perhaps, when once established, by the advancing line of constriction itself. It is attended by and dependent on the simultaneous presence of two opposed conditions—excitation above and inhibition below the excited spot. It is possible that the slow progress of the wave may be due to the struggle between these two conditions in the region of the excited spot.

Every point, then, of the intestine is in a state of activity which can be played upon and modified by impulses arriving at it from all portions of the gut above and below, and its activity at any given time will be a resultant of these three factors, two of which are opposed to one another.

It is evident that the peristaltic contraction presents many points of resemblance with the co-ordinated movement of extension or flexion which occurs in a limb as a result of an appropriate sensory stimulus. Each such co-ordinated movement involves, as has been so ably demonstrated by Sherrington, two opposed processes—excitation and inhibition. If, for instance, the leg

be flexed in response to a painful stimulus applied to the sole of the foot, this flexion includes contraction of the flexor muscles and inhibition of the extensor muscles. If the flexor muscles be divided, it is still possible to show that the extensor muscles undergo a lengthening as the result of the application of the stimulus. In the same way, a movement of extension of the leg, in response to a particular tactile stimulus applied to the ball of the foot, can be properly carried out only by a two-fold discharge causing inhibition of the flexor muscles, and contraction of the extensor muscles. The inco-ordinated spasms which distinguish strychnine poisoning are due to the abolition of the inhibitory part of each reflex and its conversion into a contractile reaction, so that antagonistic muscles are set into contraction by one and the same sensory stimulus. The physiological purpose of a peristaltic contraction is the propulsion of a solid or semi-solid object along a tube. A simple contraction of the tube, even if propagated along its walls, would probably pass over the object, squeezing it in its course, but not effecting an onward movement. In order that the object or bolus may be moved from one end of the tube to the other, it is necessary that a process of contraction of the muscle behind it should be accompanied with a process of relaxation of the muscular walls of the tube in front of it. This is the distinguishing feature of a peristaltic contraction—a process of contraction behind the object, and a process of inhibition and relaxation in front of the object. Such a double process can be effected only by a co-ordinating centre. In the case of the œsophagus this co-ordinating centre is situated in the medulla, and the orderly progression of the peristaltic wave of inhibition *plus* contraction along the walls of the tube is dependent on the integrity of the branches of the vagus nerve by which the medullary centre is united to the gullet. Division of these nerves destroys the power of swallowing. If food be thrust by the movements of the tongue into the upper part of the œsophagus, this latter may become filled up with food. The food cannot pass into the stomach on account of the absence of the one

definite factor in the peristaltic contraction, namely, the inhibition in front of the bolus, an inhibition which involves also the cardiac sphincter of the stomach. It seems that, under normal conditions, a stimulus applied to the root of the tongue or back of the pharynx and travelling by the superior laryngeal nerves to the vagus centre in the medulla, causes a fusillade discharge from the centre along the successive fibres of the vagus, an inhibitory discharge preceding in each case the motor discharge

There is no doubt that in the intestines the nervous centre responsible for the carrying out of the peristalsis is represented by the plexuses of Auerbach and Meissner. Peristaltic contractions can be obtained after complete destruction of the central nervous system or even in the excised gut. On the other hand, they are absolutely abolished if the intestines be painted with some drug abolishing the functions of nerve-cells and fibres, such as nicotine or cocaine. We must, therefore, regard Auerbach's plexus as a lowly organised nervous system with practically one reaction, namely, that which we have formulated above as the "law of the intestines." An anti-peristalsis is never observed in the small intestine. Mall has shown that if a short length of gut be cut out and re-inserted in the opposite direction, a species of partial obstruction results, in consequence of the fact that the peristaltic waves, started above the point of operation, cannot travel downwards over the reversed length of gut. The intestine above this point therefore becomes dilated. If, however, the reactions of the local nervous system be paralysed or inhibited, a reflux of intestinal contents is quite possible, since the contractions excited at any spot by local stimulation of the muscle have the effect of driving the food either upwards or downwards; the direction of movement of the food will be that of least resistance.

Influence of Vascular Conditions on the Intestinal Movements.

—There has been very considerable divergence of opinion as to the influence of ischæmia, or asphyxia, on the intestinal movements. According to Schiff, local anæmia induced by

obstruction of the aorta evokes or strengthens intestinal contractions. Nasse and Mayer and von Basch state that obstruction of the aorta arrests the movements for a time, but that they return afterwards with increased vigour. Most observers (Betz, van Braam Houckgeest, Mall), however, agree that anæmia inhibits all the movements of the intestine—a view which I can confirm. If the rhythmical contractions of the small intestine be recorded by the insertion of a small balloon, communicating with a piston recorder, obstruction of the aorta in the chest causes an almost immediate cessation of the movements, which lasts as long as the obstruction is continued (up to 15 minutes). During this time the lever sinks slowly, *i.e.*, there is a gradual diminution of intestinal tonus. If now the obstruction be relieved, the intestines contract immediately once or twice, then pause and then recommence their rhythmic movements, the contractions increasing in force for a couple of minutes. This recommencement is associated with a considerable diminution in the diastolic volume of the intestine, *i.e.*, increased tonus.

It is probable that the discrepant statements on this subject depend firstly on the frequent occurrence of anæmia and local asphyxia, and secondly on the varying behaviour of different animals. It is a familiar experience to everyone that on opening the abdomen of a recently killed rabbit the intestines will be found in a state of active movement. In the case of the rabbit the excitatory effect of the circulation of venous blood through the intestines has been frequently pointed out (Engelmann, von Basch, etc.). In the dog the influence of venous blood is not nearly so marked, and indeed tends to check the movements rather than to augment them. If a dog be killed by any means, and the abdomen then opened, the intestines will probably be found to be absolutely quiescent, or any slight contractions which may be present speedily die away. In the dog this cessation of intestinal movements is brought about, whatever means we may adopt of producing the local anæmia. Thus, the result is the same, so far as

the intestines are concerned, whether we stop the circulation through them by obstruction of the aorta, by stimulation of the vagus, by bleeding, or by cutting into the heart. Only in the case of the first part of the duodenum have we observed the special motor effect of the vagus accompanying the cardiac inhibition. Any drugs which cause a fall of blood-pressure tend to diminish in the same degree the intestinal movements, which again recover as the blood-pressure approaches normal. The exaggeration of the contractions observed on letting the blood into the intestines after a prolonged anæmia seems to be due to the great vascular dilatation and consequent increased blood-flow in the intestines which results from the previous obstruction.

Influence of the Splanchnic Nerves.—Pflüger was the first to show that stimulation of these nerves inhibited the intestinal movements. This observation has been confirmed by almost every subsequent worker, though there has been considerable discussion as to the exact mode in which the inhibitory action is brought about. S. Mayer and von Basch ascribed the inhibitory action of the splanchnics to their vaso-constrictor influence on the intestines. According to van Braam Houckgeest, this view is negatived by the following experiment. The intestines of a rabbit are exposed to the air until they become reddened by vaso-motor paralysis. Stimulation of the splanchnics now has no effect on the blood-vessels, although the movements of the intestines are inhibited as in a normal animal. Jacobi states that the intestinal inhibitory fibres of the splanchnics take a different course from the vaso-motor fibres, and that section of the nerves running from the suprarenals to the solar plexus annuls the inhibitory action of the splanchnics without interfering with their vaso-constrictor effect.

Besides these inhibitory results, various physiologists have recorded a motor effect on stimulating the splanchnics (Schiff, Ludwig and Kupfer, Bechterew and Mislowsky, Bunch). The last-named observer has given graphic records of intestinal movements in which stimulation of the splanchnics caused in some animals augmentation, in others inhibition of intestinal

tone, and in some cases preliminary augmentation. He concludes that nerve fibres of opposed functions run in the splanchnics, and that the result obtained is due to the preponderating influence of one or other kind in the particular animal employed.

According to Ehrmann, the intestines conform to von Basch's idea of crossed innervation, the splanchnics being motor for the longitudinal and inhibitory for the circular coat. Courtade and Guyon, on the other hand, state that in an animal under normal conditions the splanchnics produce contraction of the circular and inhibition of the longitudinal coat, though they have obtained Ehrmann's results when the intestines were in an abnormal state. They conclude, therefore, that the splanchnics contain motor and inhibitory fibres for both layers of muscle.

Bechterew and Mislowsky and Bunch have investigated the spinal nerve-roots which contribute fibres through the sympathetic to the intestines. According to Bunch, nerve-fibres pass to the splanchnics from the anterior roots of the sixth thoracic to the second, third, fourth or fifth lumbar nerves, and have one cell station on their course, in the ganglia of the solar plexus.

In a preceding section I have only described the appearance of the intestines after section of both splanchnic nerves or destruction of the spinal cord or abdominal ganglia. Quite a different state of things is found in a dog in whom these nerves are intact. On opening the abdomen in a warm saline bath the intestines are seen to be collapsed and absolutely motionless. Local irritation, electrical or mechanical, either provokes no response at all, or if strong enough causes a local contraction limited to the stimulated spot. On inserting a rubber capsule distended with air under pressure and connected with a piston recorder, the lever of the recorder often remains permanently motionless. If contractions are present they are slight in extent and irregular in rhythm. Stimulation either above or below the capsule produces merely inhibition.

If both splanchnic nerves be now divided there is no immediate change, but in the course of a quarter to half an hour

the intestines gradually become more active, the previously motionless intestine commences to beat rhythmically, and any contractions which were previously present become stronger and more regular. The intestine, at the same time, becomes somewhat redder than before, owing to the vascular dilatation produced by section of the splanchnics.

These facts suggest that in the intact animal, at any rate under the conditions of my experiment, tonic or reflex influences are continually descending the splanchnic nerves, inhibiting the activity of the intestines. This conclusion is strengthened by the result of stimulating these nerves. On exciting the peripheral end of the cut splanchnic immediately below the diaphragm, the intestinal contractions being recorded by the balloon method, there is at once a complete cessation of the contractions, accompanied often by a diminution of the diastolic tone of the intestinal wall. This inhibition may outlast a short stimulation of the splanchnic. If the stimulation be, however, prolonged, the intestines after a time "escape," and recommence their contractions. The inhibitory effect generally becomes less with each succeeding stimulation, pointing to a fatigue of the inhibitory fibres.

This inhibition is, of course, accompanied by a large rise of blood-pressure caused by a constriction of, amongst others, the intestinal vessels, as shown by the pallor of the intestines. The similarity between the curve of intestinal inhibition produced by stimulation of the splanchnics, and that obtained by blocking of the aorta, at once suggests the possibility that the two conditions are produced in the same way, and that the splanchnic inhibition is merely an indirect effect of the vascular constriction and consequent intestinal ischæmia which is the result of stimulating the splanchnics. The experiments of van Braam Houckgeest cannot, in the absence of plethysmographic evidence, be regarded as a direct proof to the contrary. I believe, however, that the conclusions of this observer were correct, and that the inhibitory effect of stimulating the splanchnics is quite independent of the vascular effect. Thus, there

is absence of parallelism between the two phenomena. In some cases the rise of blood-pressure may be well marked, with very little inhibition of the intestines, while in other cases we may observe prolonged inhibition with only slight alteration of blood-pressure. If the peripheral end of the divided splanchnic on one side be stimulated repeatedly with induced currents, the changes in the blood-pressure curve are remarkably constant with each stimulation. The inhibition of the intestinal movements is, however, best marked at the first stimulation, and becomes less and less marked with each succeeding one. If the intestines are active, they may continue to contract for a few minutes after circulation has been abolished by cutting out the heart. Under these conditions stimulation of the splanchnics still produces inhibition, although it can in no way alter the state of the circulation. If the stimulation be continued for a considerable time, the intestines begin to beat, and may resume their normal rhythm, while the nerve is still being excited and the blood-vessels are strongly constricted. These inhibitory effects are produced simultaneously over the whole of the small intestine and follow almost immediately the commencement of excitation. The latent period is certainly not greater than two seconds, and is probably less. It can be observed as well in a few inches of gut ligatured at the two ends as in the uninjured intestine.

Every part of the intestine appears to receive fibres indiscriminately from the splanchnics of both sides. If a short loop of gut be isolated and its contractions recorded in any way, no difference can be observed between the effects obtained on stimulating the splanchnics on either side.

The Vagus.—A number of authors have described the vagus as the motor nerve of the intestines (Budge, Ludwig and Kupfer, Engelmann, etc.). According to van Braam Houckgeest, the vagus has no direct action on the intestines, the contractions being simply propagated from the stomach. Mayer states, however, that he has observed movements of the small and large intestine on stimulation of the vagus, even after

ligature of the duodenum. There is no doubt that under certain conditions stimulation of the vagus has no apparent effect on the intestines. Bunch only observed an effect (inhibition) once out of a large number of experiments, and was therefore inclined to deny that the vagus possessed any motor functions. Jacobi states that in the rabbit, after a few days' starvation, stimulation of the vagus is without effect unless the splanchnics, or the fibres which run from the suprarenals to the solar plexus, be divided, and hence regards these fibres and the vagi as mutually antagonistic. He states that in rabbits the intestinal fibres are conveyed chiefly in one vagus, either right or left, while the other vagus sends fibres chiefly to the stomach.

These discordant results are probably due to a failure to take into account the various disturbing influences which may affect the intestines and their response to vagal stimulation. Among the conditions which may co-operate in preventing the motor effects of the vagus, considerable importance must be ascribed to anæsthetics and narcotics, and the exposure and handling of the intestines with the circulatory changes thereby induced. More important than these factors are, however, the inhibitory influences to which, as we have seen, all parts of the intestine are subject, influences which are partly reflex in origin and are started by stimulation of any sentient surface or the intestine itself, and transmitted through the splanchnic nerves, and influences which, originating in the intestine itself, tend through the local nervous mechanism to inhibit the activity of all the lower segments of the gut. In investigating the action of the vagus, then, we must avoid, so far as possible, these disturbing factors by dividing both splanchnics, by maintaining a quiet anæsthesia without excessive a.c.e. intoxication, and by dispensing, so far as possible, with any irritating lesion of the gut above the segment, the activity of which we wish to investigate.

Division of the Vagi.—I have been unable to obtain any evidence of the existence of tonic influences passing to the intestines along the vagus nerves. In most cases section of one or both vagi is without result, either immediate or remote, on

the intestinal movements. In one experiment in which the intestinal movements had been extremely active, I observed a cessation of the movements on dividing both vagi. The diminution in the activity of the gut lasted only two or three minutes, and one cannot from this isolated result deduce any tonic activity of the vagi.

Stimulation of the Vagi.—In all experiments on the influence of the vagus on the intestines it is well to adopt the precaution recommended by Jacobi, viz., the division of both splanchnic nerves, in order to remove the tonic inhibitory impulses which pass along these nerves to the intestines. Unless otherwise mentioned, this procedure was adopted in all the experiments described in this section.

If the peripheral end of the divided vagus be stimulated in the neck, the anæmia of the intestines caused by inhibition of the heart has its usual effect, viz., a temporary diminution or cessation of the intestinal contractions. There is, however, as a rule, no change in the intestines which can be regarded as a direct consequence of the vagal stimulation.

This cardiac inhibition may be prevented by intravenous injection of 0.4 c.c. of a 1 per cent. solution of atropin. If the cardio-inhibitory fibres be paralysed in this way, and the peripheral end of either vagus be stimulated again, in nearly all cases no effect is produced. If, however, the stimulation be repeated five or six times, an effect on the intestines begins to be apparent, and becomes more marked with each succeeding stimulation. The effect is two-fold. The only change which is seen in the first *effective* stimulation is a temporary inhibition of the intestinal contractions, causing a dropping of one or two beats. In the succeeding stimulations this primary inhibition effect is followed, after a latent period varying from ten seconds to two minutes, by an augmentor effect; the beats increase in amplitude and rhythm, and the relaxation between each beat is incomplete, so that there is a great increase of diastolic tone. In many cases the excitation is so pronounced that the lumen of the gut and the balloon are obliterated altogether by a strong tonic contraction.

There is no doubt that the augmentor effects of vagal excitation are extremely susceptible to the influence of inhibitory stimuli. It is very difficult, and in most cases impossible, to evoke the augmentation unless the splanchnic nerves have been previously divided. On several occasions, when recording with the balloon in the lower part of the ileum, I have found that an absence of effect, even on repeated stimulation, was associated with a distended condition of the duodenum or upper part of the small intestine. On relieving the distension by means of a small incision in the unattached border of the gut, and then stimulating the vagus again, a motor effect was immediately produced. It seems probable, therefore, that the absence of the augmentor effect in a loop of intestine which has been ligatured above or at both ends, is due not so much to the cutting off of the normal nerve channels as to the continued inhibition excited by the upper ligature. I am inclined, therefore, to believe that the vagus as well as the splanchnic impulses reach the gut by way of the mesenteric nerves.

Ileo-colic Sphincter.—As a result of the two sets of movements described above, the food is thoroughly mixed with the digestive juices, and the greater part of the products of digestion are brought into contact with the intestinal wall and absorbed. What is left—a proportion varying in different animals according to the nature of the food—is passed on by occasional peristaltic contractions through the lower end of the ileum into the colon, or large intestine. The lowest two centimetres of the ileum present a distinct thickening of its circular muscular coat forming the ileo-colic sphincter. This sphincter relaxes in front of a peristaltic wave, and so allows the passage of food into the colon. On the other hand, it contracts, as a rule, against any regurgitation which might be caused by contractions in the colon. Although thus falling into line with the rest of the muscular coat, as concerns its reaction to stimuli arising in the gut above or below, it presents a marked contrast to the rest of the gut in its relation to the central nervous system. It is apparently unaffected by stimu-

lation of the vagus. Stimulation of the splanchnic, however, which causes complete relaxation of the lower part of the ileum with the rest of the small intestine, produces a strong contraction of the muscle fibres forming the ileo-colic sphincter.

It is interesting to note that the same effect is produced by the injection of adrenalin, which causes relaxation of the whole of the rest of both of the small and of the large intestine. This small portion of the muscular wall of the intestine seems to be distinct in its origin from both the small and the large intestine. It is not affected by stimulation of the pelvic visceral nerves, which supply motor fibres to the colon, and is apparently controlled simply by the sympathetic system.

PART V.

ABSORPTION OF THE FOOD-STUFFS FROM THE SMALL INTESTINE.

1. *The Absorption of Water and Saline Fluids.*—As the result of the various processes of digestion, all the ingesta are finally reduced to a condition in which they are soluble for the most part in water and in all cases in the fluids of the alimentary canal. Thus, the carbohydrates are reduced to soluble sugars, the proteins—soluble or insoluble—to soluble amino-acids, and the fats are converted either into soluble soaps or into substances such as insoluble soaps and fatty acids, which are soluble in bile. In the following pages we have to discuss the channels of absorption of these various constituents of the food, the conditions in which they are absorbed, and the mechanism, intracellular or otherwise, which determines their passage from the lumen of the gut into the body fluids. In considering the general question as to the forces which are concerned in the passage of these substances from the inner to the outer wall of the gut, it will be convenient to deal with the subject under its simplest aspect. In our first section, therefore, namely, the

absorption of water and salts, we may include in our discussion the general question as to the mechanism of absorption by the alimentary canal.

The intake of water, and probably of salts, by the alimentary canal, in accordance with the requirements of the organism as a whole, seems to be regulated almost entirely by the central nervous system, the higher parts of this system, viz., those concerned with appetite, being particularly involved in the process. Thus, in man we find that any large loss of fluid to the body, as by sweating, diarrhoea, hæmorrhage, gives rise to an intense thirst that has its natural reaction in increased intake of water by the mouth. On the other hand, the property possessed by the alimentary canal of absorbing water and weak saline fluids contained in its interior is very little influenced by the state of depletion, or otherwise, of the water depots of the body. Our own experience, again, tells us that it is practically impossible, however large the quantities of fluid that we ingest, to evoke the production of fluid motions, and that the greater part of the ingested fluid is absorbed on its way through the alimentary canal.

Thus, a man may keep himself in perfect health and maintain the water content of his body whether he take one litre or six litres of water daily. The whole process of regulation, apart from that determined by appetite, appears to be carried out at the other end of the cycle, viz., by the kidneys. As concerns absorption of water, there is no chemical solidarity between the alimentary surface and the rest of the body. Whenever water is presented to the surface it is absorbed and passes into the circulation.

The case is different if large quantities of concentrated saline fluid be ingested, especially if the salts be other than sodium chloride. Certain groups of salts present greater resistance to absorption than others; among them we may mention the tartrates and the sulphates, and it is among these, therefore, that our chief saline purgatives are found. But in every case absorption by the alimentary surface is a question of the

local conditions rather than of the needs of the organism as a whole. Only in extreme hydræmic plethora, when the intestinal wall is swollen with exuded fluid, may we observe a distinct hindering of the process of absorption or actual conversion of absorption into secretion. Such a condition of hydræmic plethora as is produced in animal experiments by the injection of huge quantities of normal solution into the circulation, probably never occurs in the normal intact animal.

In this chapter we have, therefore, to discuss the nature of the local conditions in the alimentary canal which determine the absorption of water from this viscus. This question is narrowed by the fact, which has been established beyond doubt by the researches of von Mering, Edkins and others, that the absorption of water in the stomach may be regarded as nil. Although from this viscus alcohol, peptone, and sugar may be absorbed to a certain slight extent, water or saline fluids introduced into it are passed through the pylorus either without change or with their quantities added to by the secretion of fluid from the gastric glands. In no case is there a diminution of fluid in the stomach.

In fact, according to Pfeiffer, all solutions introduced into the stomach in man finally acquire a molecular concentration less than that of the blood plasma. Whereas the normal depression of freezing-point of blood plasma is about 0.56 C., Pfeiffer found that fluids which had been some time in the stomach acquired a depression of freezing-point of 0.45 C. Fluids with a smaller tonicity underwent concentration as a result of the secretion into them of salts. Fluids isotonic with the plasma were diluted, and this secretion of water was still more marked in the case of certain solutions, such as cane sugar, which underwent dilution in all cases whether hypo- or hypertonic.

The chief absorption of water occurs in the small intestine. It is on this account that the salient features of cases of dilatation of the stomach with stenosis, absolute or relative, of the pyloric orifice can be nearly all referred to the starvation of the body in water, and can be often relieved by the administra-

tion of water either subcutaneously or by the rectum, *i.e.*, by the channels through which absorption is still possible. The introduction of water into the stomach simply increases the dilatation, but does not relieve the intense thirst of the patient. Water that has been swallowed to quench thirst has first to be passed from the stomach into the small intestine before it can be absorbed and relieve the needs of the tissues.

Absorption of water also occurs in the large intestine. The intestinal contents at the ileo-cæcal valve contain relatively nearly as much water as they do at the upper part of the jejunum. Their absolute bulk is, however, much smaller, so that only a small proportion of the water that has been taken in by the mouth remains to be absorbed in the large gut, an amount probably inferior to that which has been added to the contents of the small intestine in the form of secretion by the stomach, liver, pancreas, and intestinal tubules.

The main problem before us is, therefore, the mechanism of absorption of water and saline fluids by the villi of the small intestine. By means of these structures the absorbing surface of the intestine is enormously increased. It has been calculated that each square millimetre of intestine represents an absorbing surface of 3 to 12 mm. Each villus consists of a framework of reticular tissue containing many leucocytes in its meshes, separated from the lumen of the gut by a continuous layer of columnar epithelial cells. These cells rest on an incomplete basement membrane, and each presents on the side turned towards the lumen of the gut a striated basilar border. Each villus contains two channels, by means of which material, passing from the inner to the outer side of the epithelium, may be carried into the general circulation. In the centre of the villus we find the central lacteal, a club-shaped vessel bounded by a complete layer of delicate endothelial cells. This lacteal leads into a plexus of lymphatics placed superficially to the muscularis mucosæ. From this superficial plexus, communicating branches pass vertically to a corresponding plexus lying in the sub-mucosa. The central lacteal and the superficial plexus are

free from valves, but these structures are present in abundance in the deeper plexus, so that no reflux into the lacteal is possible. From the *muscularis mucosæ*, unstriated muscle fibres pass up through the villus to be attached partly to the outer surface of the central lacteal, partly by expanded extremities to the basement membrane covering the surface of the villus. It is evident that contraction of these muscle fibres will tend to empty the central lacteal into the deep plexus of lymphatics, and may also cause an expulsion of the contents of the spaces of the retiform tissue of the villus into the central lacteal. We have no reason to regard the contractions of these muscle fibres as *necessary* for any circulation of lymph through the apparatus just described. The alimentary canal represents one of the few localities where a constant formation of lymph is proceeding, even in a condition of complete rest. On placing a cannula in the thoracic duct of a dog, we obtain an outflow of lymph which may vary in different animals between 1 c.c. and 10 c.c. in the ten minutes. No alteration is produced in the lymph flow by cutting off the access of lymph from the limbs or from the kidneys. Ligature of the lymphatics from the liver may reduce the flow by a third, but never entirely abolishes it, and very often leaves the flow unaffected. Ligature of the duct above the abdominal viscera stops the flow absolutely. We are, therefore, justified in concluding that the greater part of the lymph obtained from the thoracic duct is derived from the alimentary canal, and therefore that in this viscus, and probably in the villi themselves, the transudation of fluid from the blood capillaries into the tissue spaces, and from here into the lymphatics, is continually going on, so that any of the intestinal contents which had made their way into the spaces of the villus might be entrained in this lymph current and carried away with it into the thoracic duct, and so into the general blood system.

The other possible channel of absorption is by the capillary blood vessels of the villus. Each villus is supplied with blood from one or two arterioles, which break up into a rich plexus of capillaries lying close under the basement membrane of the

villus. The blood from this is collected into one or two veins, and joins the radicals of the portal vein in the sub-mucosa and in the mesentery. In these capillaries the blood is circulating rapidly, so that a considerable amount of material may pass into them from the spaces of the villus within, say, one hour, without altering appreciably the percentage composition of the blood. On the other hand, it must be remembered that the blood in these vessels is at a high pressure, probably not less than 30 mm. hg., so that any absorption into the blood stream must occur against this pressure. It is probable, therefore, that in explaining any absorption by the blood vessels we shall have to place out of count any possibility of the passage occurring in consequence of hydrostatic differences of pressure, *i.e.*, by a process of filtration.

In the absorption of water and saline fluids from the gut, we may neglect the lymph channels altogether. It has been shown by Heidenhain that when salt solutions are introduced into the small intestine they are rapidly absorbed without the production of any corresponding increase in the rate of lymph flow from the thoracic duct. Thus, in one experiment, 280 c.c. of serum were introduced into the small intestine. Fifty minutes later it was found that 190 c.c. of the serum had been absorbed. During this time the lymph from the thoracic duct had shown a slight increase, but the total amount obtained during this time only amounted to 33 c.c., representing an excess of 15 c.c. over that obtained during an equal space of time before the introduction of the serum. Moreover, if two comparative experiments be carried out, in one of which the thoracic duct is ligatured and in the other free, no difference will be found in the two animals between the times taken for the absorption of equal amounts of normal saline fluid from the lumen of the intestine. On the other hand, introduction of large amounts of fluid into the small intestine may cause an actual diminution of the solids of the plasma, so that we are justified in regarding the capillary network of blood vessels at the surface of the villi as solely responsible for the absorption of fluids from the intestine.

The problem which lies before us is to determine what are the forces which cause this transference of fluid and dissolved substances from one side to the other of the membrane, composed of epithelial cells, *plus* capillary endothelium. As in all similar questions, *e.g.*, in dealing with the secretion and formation of lymph, we have, in the first place, to decide whether the forces at work have their seat within or outside the cells of which the membrane is composed. Before we can come to a conclusion on this point, we must know what are the possibilities of transference across a dead membrane, *i.e.*, one in which there is no energy available for the process in consequence of chemical changes occurring within the membrane itself, or within the units of which the membrane is composed. Let us consider what are the factors which may determine the passage of fluid and dissolved substances across such a membrane. In the statement of the problem originally made by Heidenhain, various factors are neglected which have to be taken into account in any discussion of the physiological conditions involved.

Heidenhain's statements are as follows:—

1. If two watery solutions with the same osmotic pressure are separated by a membrane through which diffusion can take place, no change occurs in volume on either side of the membrane.

2. If the solutions on either side of the membrane are of unequal osmotic pressure, water passes from the side where the pressure is less to the side where the osmotic pressure is greater.

3. The osmotic pressure of a solution is equal to the sum of the partial pressures of the various dissolved substances.

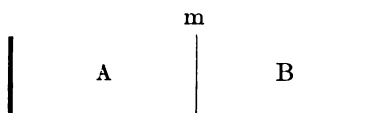
4. If the solutions on the two sides of the membrane have the same total osmotic pressure, but unequal partial pressures of their various constituents, each constituent of the solution passes from the side where it has the higher partial pressure to the other side. No change in the volume of water on the two sides takes place.

Of these four statements only one (No. 3) is absolutely correct. The other three are only correct under certain defined conditions which are rarely fulfilled in the body.

In the phenomena of transference of fluid or dissolved substances across a membrane, the nature of the membrane itself is all-important. I will, therefore, shortly summarise the various modes in which interchanges may take place across membranes of varying permeability. We shall see that the close analogy which exists between substances in solution and gases, when dealing with "semi-permeable" membranes, is also borne out by experiment when used to predict the behaviour of solutions separated by such permeable membranes as occur in the body.

The simplest case is that in which two fluids are separated by a perfect semi-permeable membrane that permits the passage of water, but is absolutely impermeable to dissolved substances. In this case the transference of water from one side to the other depends entirely on the difference of osmotic pressure between the two sides.

If we suppose two vessels, A and B, separated by such a membrane, A containing a solution of *a* and B a solution of *b*, water will pass from A to B so long as the osmotic pressure of *b* is greater than the osmotic pressure of the solution *a*. If B be subjected to a hydrostatic pressure greater than the osmotic difference between the two fluids, water will pass from B to A until the force causing filtration or transudation (the hydrostatic pressure) is equal to the force causing absorption into B



(the difference of osmotic pressures). Under no circumstances will there be any transference of salt or dissolved substance between the two sides. Such semi-permeable membranes as this, however, rarely occur in the body. It is possible that the external layer of the cell-protoplasm may in some cases resemble the protoplasmic pellicle of plant-cells in possessing this "semi-permeability," but in nearly all cases where we have a membrane made up of a number of cells, it can be shown that such a membrane permits the free passage of, at any rate, a large number of dissolved substances.

Let us now consider what will occur when the two solutions A and B are separated by a membrane which permits the free passage of salts and water. If the osmotic pressure of B be higher than A at the commencement of the experiment, the force tending to move water from A to B will be equal to this osmotic difference. But there is, at the same time, set up a diffusion of the dissolved substances from B to A and from A to B. The result of this diffusion must be that there is no longer a sudden drop of osmotic pressure from B to A, and the result of the primary osmotic difference on the movement of water will be minimised in proportion to the freedom of diffusion which takes place through the membrane. Now let us take a case in which A and B represent equi-molecular and isotonic solutions of *a* and *b*. It is evident that the movement of water into A will vary as $A_p - B_p - O$. But diffusion also occurs of *a* into B and of *b* into A. Now the amount of substance diffusing from a solution is proportional to the concentration, and therefore to its osmotic pressure, as well as to its diffusion coefficient. Hence the amount of diffusing into B will vary as $A_p.k$ (when *k* is the diffusion coefficient).

In the same way, the amount of diffusing into A will vary as $B_p.k'$.

Hence, if *k* is greater than *k'*, *i.e.*, if *a* is more diffusible than *b*, the initial result must be that a greater number of molecules of *a* will pass into B than of *b* into A. Hence, the solutions on the two sides of the membrane will no longer be equi-molecular, but the total number of molecules of *a* in B will be greater than the number of molecules of *b* in A, and this difference will be most marked in the layers of fluid nearest the membrane. The result, therefore, of the unequal diffusion of the two substances is to upset the previous equality of osmotic pressures. The layer of fluid on the B side of the membrane will have an osmotic pressure greater than the layer of fluid in immediate contact with the A side of the membrane, and there will thus be a movement of water from A to B. Hence, if we have two equi-molecular and isotonic solu-

tions of different substances separated by a membrane permeable to the dissolved substances, there will be an initial movement of fluid towards the side of the less diffusible substance.

We have an exact parallel to this in Graham's familiar experiment in which a porous pot filled with hydrogen is connected by a vertical tube with mercury. In consequence of the more rapid diffusion outwards of the hydrogen than of atmospheric air inwards, the pressure within the pot sinks below that of the surrounding atmosphere, and the mercury rises several inches in the tube. We must therefore conclude that even when the two solutions on either side of the membrane are isotonic, there may be a movement of fluid from one side to the other with a performance of work in the process.

Osmosis may even occur from a fluid having a higher osmotic pressure *towards* a fluid having a lower osmotic pressure. If, for example, equi-molecular solutions of sodium chloride and glucose be separated by a peritoneal membrane, the osmotic flow will take place from the fluid having the higher osmotic pressure—sodium chloride. We might compare with this experiment the results of separating hydrogen at one atmosphere's pressure from oxygen at two atmospheres' pressure by means of a plate of graphite. In this case the initial result will be a still further increase of pressure on the oxygen side of the diaphragm—a movement of gas against pressure taking place in consequence of the greater diffusion velocity of hydrogen.

So far we have only considered the behaviour of solutions when separated by a membrane, the permeability of which to salts is comparable to that of water; so that the passage of salts through the membrane depends merely on the diffusion rates of the salts. There can be no doubt, however, that we might get analogous movements of fluid against total osmotic pressure determined, not by the diffusibility of the salts, but by the permeability of the membrane for the salts—a permeability which may depend on a state of solution or attraction existing between membrane and salts. We have a familiar analogue to such a condition of things in the passage of gases through

an india-rubber sheet. If two bottles, one containing carbonic acid, the other hydrogen, be separated by a sheet of india-rubber, CO_2 passes into the hydrogen bottle more quickly than hydrogen can pass out into the CO_2 bottle, so that a difference of pressure is created between the two bottles, and the rubber bulges into the CO_2 bottle. The importance of the membrane in determining the direction of the osmotic pressure of fluid is well illustrated by Raoult's experiments. When alcohol and ether were separated by an animal membrane, alcohol passed into the ether, whereas if vulcanite were employed for the diaphragm, the osmotic flow was in the reverse direction, and an enormous pressure was set up on the alcohol side of the diaphragm.

It has often been assumed that the main factor in determining the permeability of a membrane is its physical structure, and especially the coarseness of its grain or the size of the borders, actual or potential, which this presents. There is no doubt that the passage of substances through a membrane under pressure is determined to a certain extent by the density of the membrane. Thus, Bechhold has shown that by using celloidin membranes of different concentration it is possible to obtain membranes of variable permeability, and by their means to separate coagulable proteins into various groups, and these again from substances such as albumoses and peptones. Far more important, however, in the case of the colloidal membranes which are of physiological interest, is the chemical character of the material of which they are composed. The chemical character, *i.e.*, the molecular structure of the material, must be regarded as responsible for the power of the membrane to imbibe fluids, to *adsorb* dissolved substances, the adsorption varying according to the chemical character of the substances in question. Thus, the crystalline carbohydrates, such as grape sugar, etc., are easily soluble in water, but slightly soluble in alcohol, and practically insoluble in ether and benzol. The amorphous carbohydrates, *e.g.*, starch, cellulose, etc., which must be regarded as derived by a process of condensation from the crystalline carbohydrates,

though insoluble in water, have a strong power of imbibing this fluid. This power may be limited, as in the case of cellulose, or may be unlimited, as in the case of gum arabic, so that a so-called solution results. Only in the case of limited imbibition is it possible for a membrane to persist as a medium of diffusion or filtration. These bodies swell up but slightly in alcohol, and are unaffected by ether and benzol. On the other hand, india-rubber and the various resins take up ether, benzol, and turpentine, often to an indefinite extent, while they are untouched by water, a behaviour comparable with the easy solubility of the hydro-carbons, aromatic acids, and esters in ether and benzol, and their insolubility in water. As Overton has pointed out, the power of amorphous carbohydrates to take up fluids is altered by changing their chemical structure in the same direction as the solubility of the corresponding crystalline carbohydrates. Thus, if the hydroxyl groups in the sugars be replaced by nitro-, acetyl-, or benzol- groups, they become less soluble in water, while their solubility in alcohol, acetone, etc., is increased. In the same way, the replacement of the hydroxyl groups in cellulose by NO_2 groups diminishes the power of this substance to take up water, but renders it capable of swelling or dissolving in alcohol, acetone, etc. It is probable that the behaviour of membranes to various substances will also differ according to the solubility of the latter in the membrane or in the fluid which the membrane has imbibed.

The passage of dissolved substances through the membrane may, however, be markedly affected by the power of the membrane to adsorb these substances. Thus, if sodium chloride solution be passed under pressure through a gelatin film, the first drops of filtrate are poorer in this salt than the original fluid owing to the absorption of NaCl by the gelatin. When the film has adsorbed its maximum amount of salt, *i.e.*, the amount which is in equilibrium with the strength of solution presented to it, the solution will then pass through in its original strength. This process of adsorption may, however, alter the properties of the membrane so that its behaviour under given circumstances

is a function of the time during which these circumstances are operative. This is especially marked where the adsorption affects chiefly the colloidal constituents of the filtering fluid. On the other hand, the power of a membrane to adsorb colloids may enable these substances to be passed through such a membrane more easily than they would through an equivalent thickness of water.

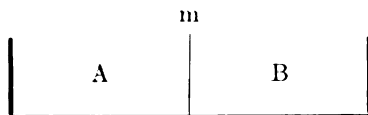
There seems little doubt that one of the main factors in determining adsorption by a colloid is the electrical charge which its constituent particles possess in relation to the surrounding medium. An electrically charged particle will tend to adsorb all colloids of an opposite charge and precipitate them on its surface.

If a constant difference of potential be maintained between the two sides of a membrane it would be possible for such a membrane to present an irreciprocal permeability. A familiar example of such a membrane is presented by the well-known cell used as a rectifier of alternating currents, in which a colloidal membrane of alumina, formed by the passage of the current serves to stay the further progress of the Al^{III} ions, and therefore to prevent the passage of the current in the same direction. With reversal of the current, the membrane (which is of molecular dimensions) is instantaneously dissolved, and the current passes.

Irreciprocity of permeability has often been assumed as a possible explanation of the phenomena presented by many living cells, as regards the functions both of secretion and absorption. Such a membrane, directly it begins to operate, would create a difference of electrical potential between the two sides of the membrane in such a direction as to oppose the passage of the substance to which the membrane was permeable in the one direction. In order, therefore, to maintain a continual passage in one direction, a continual expenditure of energy would be necessary in order to overcome this difference of potential. We could make a membrane apparently irreciprocal by passing a current through it in the right direction, but this

again would require expenditure of energy. Wherever, therefore, in the body we find that an absorbing membrane presents irreciprocal permeability, we must assume that energy is being spent on or within the membrane, and if the membrane consists of living cells we are justified in referring the source of this to chemical changes taking place in the cells. We should say that the absorption was due to the vital activity of the cells, and not to the more mechanical processes of filtration and osmosis. By such a statement we do not mean that the ordinary physical laws are abrogated for the process to take place, but that energy is expended in maintaining the passage of some fluid or dissolved substance, which energy has its seat of origin in the living cells themselves.

The next point to be considered is the passage of a dissolved substance across membranes in consequence of differences in the partial pressure of the substance in question on the two sides of the membrane. Great stress was laid by Heidenhain and his pupil Orlow on the fact that from the peritoneal cavity, as well as from the intestine, salt may be taken up from fluids containing a smaller percentage of this substance than does the blood plasma, and they regard this absorption as pointing indubitably to an active intervention of living cells in the process. This argument requires examination. Supposing the two vessels A and B to be separated by a membrane which offers free passage to water and a difficult passage to salts. Let A contain .5 per cent. salt solution and B a solution isotonic with a 1 per cent. NaCl, but containing only .65 per cent. of this salt, the rest of its osmotic tension being due to other



dissolved substances. If the membrane were absolutely "semi-permeable," water would pass from A to B until the two fluids were isotonic, i.e., until A contained 1 per cent. NaCl (we may regard volume B as infinitely great to simplify the argument).

If, however, the membrane permitted passage of salt, the course of events might be as follows: At first, water would pass out of A, and salt would diffuse in until the percentage of NaCl in A was equal to that in B. There would now be an equal partial pressure of NaCl on the two sides of the membrane, but the total osmotic pressure of B would still be higher than A. Water would, therefore, still continue to pass from A to B more rapidly than the other ingredients of B could pass into A. As soon, however, as more water passed only from A, the percentage of NaCl in A would be raised above that in B. The extent to which this occurs will depend on the impermeability of the membrane. As soon, however, as the NaCl in A reaches a certain concentration it will pass over into B, and this will go on until equilibrium is established between A and B. Extending this argument to the conditions obtained in the living body, we may conclude that neither the raising of the percentage of a salt in any fluid above that of the same salt in the plasma, nor the passage of a salt from a hypotonic fluid into the blood plasma, can afford in itself any proof of an active intervention of cells in the process.

We have already seen that the *effective* osmotic pressure of a substance, *i.e.*, its power of attracting water across a membrane, varies inversely as its diffusibility, or as the permeability of the membrane to it. What, then, will be the effect, supposing that on one side of the membrane we place some substance in solution to which the membrane is impermeable?

We will suppose that A and B contain 1 per cent. NaCl, but that B contains in addition some substance X to which the membrane is permeable. Since the osmotic pressure of B is higher, by the partial pressure of X, than that of A, fluid will pass from A to B by osmosis. But the consequence of this passage of water will be to concentrate the NaCl in A, so that the partial pressure of this salt in A is greater than in B. NaCl will, therefore, diffuse from A to B, with the result that the former difference of total osmotic pressure will be re-established. Hence, there will be a continual passage of both

water and salt from A to B, until B has absorbed the whole of A. This result will be only delayed if the osmotic pressure of A is at first higher than B, in consequence of a greater concentration of NaCl in A. There may be at first a flow of fluid from B to A, but as soon as the NaCl concentration on the two sides has become the same by diffusion, the power of X to attract water from the other side will make itself felt, and this attraction will be proportional to the osmotic pressure of X.

In the living body the substance "X" may be represented by the colloidal proteins of the blood plasma. Those, as I have shown, may possess a definite osmotic pressure of about 30 mm. Hg. This pressure, though small, would be sufficient to determine the absorption of any salt solutions into the blood stream, provided that the membrane separating the blood from the salt solutions was permeable to water and salts, but impermeable to the protein contents of the blood plasma.

In endeavouring to apply the principles just laid down to the discussion of the mechanism of absorption in the intestinal villus, we have, in the first place, to inquire into the physical conditions of the absorbing membrane itself. The main constituent of this membrane is a continuous layer of living epithelial cells. These cells, to judge from their behaviour when isolated, must be assumed as constituted on their inner surface, *i.e.*, that turned towards the lumen of the gut, in a manner comparable to that which holds for most of the isolated animal and vegetable cells which have so far been the subject of study. This limiting membrane must, therefore, be regarded as lipid in character, *i.e.*, as composed of some complex of lecithin and cholesterin, and permeable only by such substances as are soluble in lipoids. On the other hand, it is possible that the substance connecting the cells together, and constituting the thin layer of intercellular cement substance, may be of a different nature and possibly permeable by substances in watery solution. We have, therefore, to consider what is the way actually traversed by the substances which we know can be absorbed by the gut. Do they enter the blood circulation through the cells or between

the cells? Water could, of course, pass in either direction. Most of the inorganic salts, however, such as sodium chloride, are insoluble in lipoids, and would therefore have to pass, so far as their solubility is concerned, between the cells.

A number of experiments have been made by Höber to determine the path taken by various substances in solution on absorption by the lining membrane of the gut. In order to be able to trace these substances on their way through the intestinal epithelium, he made use of dye substances which are known to be taken up and absorbed into the blood stream when introduced into the gut. Of these dyes some, such as methylene blue, toluidine blue, and neutral red, are soluble in lipoids. Others, especially sulphonic derivatives of these dyes, are insoluble in lipoids, but freely soluble in water. Höber found that the lipid-soluble dyes were taken up by the cells, and in these could be detected on microscopic examination as minute coloured granules. The water-soluble dyes, on the other hand, though absorbed from the gut, could never be detected in the epithelial wall, and, therefore, were assumed by him to have passed through the intercellular cement substance in a condition too dilute for microscopic detection. One experiment Höber adduces as showing that the path of neutral salts lies between the cells. If, after the administration of neutral red or toluidine blue, the intestinal mucous membrane be placed while living into ammonium molybdate solution, the cells are found to be free from granules, and all the colouring matter is accumulated in a precipitated form between the cells. Höber explains this result as showing that the ammonium molybdate passed into the intercellular spaces, precipitated any dye-stuff there, and gave rise to diffusion currents, so that the dye within the cells passed out into the intercellular spaces where it was at once precipitated. It is worthy of note that all these substances are abnormal as far as the body is concerned. We cannot imagine that at any time in the course of evolution of the properties of the intestinal epithelium, the cells were ever presented with or had to discriminate under normal vital conditions between different dye-

stuffs, whether lipoid-soluble or not. The behaviour of these dyes might, therefore, be determined entirely by the physical conditions of the cell membrane, without necessarily involving a similar behaviour of the cells towards the normal constituents of the food. Even in Höber's experiments the physical conditions of the epithelial cells fail to account for their varying behaviour towards different metallic salts. It was shown by Hochhaus and Quincke that iron salts, when administered, were absorbed in the duodenum, and gave rise in the cells lining this part of the intestine to the appearance of granules giving a distinct iron reaction. Höber confirms this statement, but finds that no other metallic salt, such as gold or mercury, behaves in the same way, although there is no physical difference between the solubilities of these salts and that of the iron salts. And indeed it is quite legitimate to assume that the lipoid membrane or limiting layer round every cell has as its main office, not the regulation of the access of food-stuffs to the cell, but the protection of the cell from any of the food-stuffs which it does not require for its metabolism. If it were not for such a membrane the assimilation of a salt would be determined entirely by the concentration of the food-stuffs in its immediate surroundings, whereas we know that the assimilation of any organism, whether uni- or multi-cellular, is determined, in the first place, by the internal processes occurring in the living organism itself. According to these processes, and the needs thereby induced, the uptake of food material may be large or small whatever the concentration of this material in the surrounding medium. It would, indeed, seem strange that the whole absorbing surface of the intestine should be covered by a membrane of which the greater part was useless for the absorption of the common food-stuffs, as would be the case if these could only penetrate the membrane by the narrow chinks between the cells. It seems, indeed, more probable that the absorption of the different food-stuffs, and probably also of the normal salts of the body, is effected by the cells themselves, in accordance with their nutritional needs, and this view is

strengthened when we come to examine into the forces involved in the process of absorption even of normal saline solutions. This subject has been specially investigated, in the first place, by Heidenhain, and more lately by Waymouth Reid and Cohnheim. We may examine certain of their experiments in the light of the principles laid down earlier.

The experiments by these observers have reference to the absorption of serum and of dilute salt solutions from a loop of intestine in as normal a condition as possible, as well as from such loops in which the epithelium had been subjected to the action of some poisoning agent, such as sodium fluoride or arsenic. If 50 c.c. of normal sodium chloride solution be introduced into a loop of intestine, it is found to be absorbed steadily, so that at the end of an hour not more than about 20 c.c. may be recoverable. The absolute amounts absorbed differ in various experiments, but are fairly uniform for repeated observations on one and the same animal. The absorption of such a solution could be ascribed to the osmotic pressure of the colloids in the blood plasma or lymph within the spaces of the villi. If instead of using isotonic solutions, hypertonic solutions are employed, *e.g.*, a 2 or 3 per cent. NaCl solution, absorption still takes place, but may be preceded by an interval in which there is an actual increase of the fluid contained in the gut. Here, again, we might ascribe the absorption to the physical factors present were it not that absorption is found to commence before the fluid in the gut has attained isotonicity with the blood. In fact, employing a 1.5 per cent. salt solution, absorption may occur from the very beginning of the experiment. If such a solution is passed through the epithelial membrane into the blood plasma with a smaller tonicity, it is evident that work must be done in the process, work which can only be furnished by the cells of the epithelium. When sugar solutions are employed they behave in somewhat similar fashion to sodium chloride solutions, provided that the sugar is one of the absorbable hexoses, both sugar and water being rapidly absorbed. It is important to note that dextrose is absorbed from

the gut almost as rapidly as sodium chloride, and quite as rapidly as sodium iodide, although its diffusibility is very considerably less than either of these salts. Moreover, great differences are found between the rate at which different sugars are absorbed, differences which are not referable to the diffusibility of the sugars in question. Thus, the mono-saccharides, glucose, fructose, galactose, are absorbed with double the rapidity of solutions of cane sugar and maltose, and it seems that in the absence of hydrolytic splitting of the disaccharides, absorption from the gut would be entirely abolished. Thus, lactose disappears from the intestine much more slowly than either of the other two disaccharides, so that large doses may give rise to a laxative effect. In animals devoid of lactase, the lactose-splitting ferment, in their intestinal epithelium, milk sugar is apparently not absorbed at all.

The most cogent argument, perhaps, in favour of an active intervention of the cells of the gut in the process of absorption is furnished by the study of the absorption of blood serum. It was shown both by Heidenhain and by Waymouth Reid that if an animal's own serum be introduced into a loop of its intestine, the serum undergoes absorption. This absorption affects the water and salts more than the protein, so that the percentage of the proteins in the fluid remaining in the intestine is increased. In this case the fluid within the gut is identical with the fluid within the blood vessels. There are no differences in concentration, quality of salts, or osmotic pressure of proteins. Nevertheless, water passes through the cells of the gut from their inner to their outer sides entraining with it the salts of the serum and a certain proportion of the indiffusible proteins. It is impossible to explain this result as due to the digestion of the proteins and their conversion into diffusible products, since the intestinal loops were washed free of any trypsin that they contained, and serum has itself a strong antitryptic action which would prevent its being attacked by even a strong solution of trypsin.

The active intervention of the cells in the absorption of salt solutions as well as of serum can be abolished by any means which diminishes or destroys their vitality, such as the addition of sodium fluoride to the fluid to be absorbed, as in the experiment just quoted, or destruction of the epithelium by previous temporary occlusion of the blood vessels supplying the loop of intestine.

The epithelial cells of the intestine must, therefore, be actively involved in the absorption of fluid, *i.e.*, a certain proportion of the energy set free within them by the oxidation of their food-stuffs must be employed in the pumping of water and salts from one side of the cell to the other. This conclusion is confirmed by certain experiments by Reid and Cohnheim, in which two identical solutions of sodium chloride were separated from one another by a membrane consisting of the whole living intestinal wall. In these experiments it was found that there was active transference from the inner to the outer side of the membrane.

We must conclude that, when a fluid is introduced into the intestine, an active transference of water from the lumen into the blood stream is affected by the intermediation of forces having their origin in the metabolism of the cells themselves. This work of absorption of the cells may be aided or hindered according to the physical conditions present. If these act against the cells, *e.g.*, if the fluid be hypertonic, the absorption is effected more slowly, while with hypotonic solutions, the physical conditions concur with the vital activity of the cells in bringing about a very rapid transference of fluid from the gut into the blood vessels. Among these physical conditions we must reckon the nature of the salts present in the solution. If these can pass easily into and through the cells, *e.g.*, ammonium salts, or sodium chloride, absorption is carried out rapidly. If, on the other hand, the salts in the intestinal contents are but slightly diffusible, or have very little power of penetrating into the cells, the absorption of water by the cells causes an increased concentration of the salts, and therefore an increased osmotic

pressure, which offers a resistance to any further absorption, and the process comes to an end when the absorptive power of the cells is exactly balanced by the increased osmotic pressure, or attraction for water, of the intestinal contents.

We must, therefore, ascribe absorption of fluids by the intestines to the activity of the cells clothing the villi. The effectiveness of this activity will be influenced by the osmotic pressure and the quality of the solutions involved, just as the results of the contractions of our muscles will differ according to the resistance which the contractions have to overcome.

One fact comes out in all these experiments on the absorption of NaCl solutions, namely, the extraordinary difference in the ease with which this salt passes from within outwards, or from without inwards, through the intestinal epithelium. This epithelium, in fact, seems to be endowed with an irreciprocal permeability, salt passing with extreme facility from the lumen of the gut into the blood vessels, although it is difficult, apart from the secretion of succus entericus, to detect any passage from the blood into the intestinal contents.

When we study the relative absorbabilities of different salt solutions, we find variations in the rapidity with which they are absorbed, variations which have apparently no relation to the diffusibility of the salts in question. Cushny and Wallace, as the result of their experiments on the relative absorbability of salt solutions from the gut, divide the salts into four main classes, as follows:—

I.	II.	III.	IV.
Sodium chloride, bromide, iodide, formate, acetate, propionate, butyrate, valerianate, caprate.	Ethyl sulphate, nitrate, lactate, salicylate, phthallate.	Sulphate, phosphate, ferrocyanide, caprylate, malonate, succinate, malate, citrate, tartrate.	Oxalate, fluoride.

Of these, the first class contains those salts which are absorbed with great ease from the intestine. The second group of salts are absorbed with somewhat greater difficulty. The third group are absorbed so slowly, *i.e.*, the salts retain the water in which they are dissolved so long, that they increase peristalsis and act

as laxatives or purgatives. The members of the fourth class are not absorbed at all. It is evident that this classification is independent of the diffusibility of the salts. Sodium acetate has a much smaller disassociation value and a lower diffusibility than sodium chloride or iodide, and yet is absorbed at approximately the same rate as these two salts. There is, however, as Cushny pointed out, one physical or chemical character which apparently determines the non-absorbability (relative or absolute) of the members of the third and fourth class. All these salts normally form with calcium insoluble compounds. This common character is not, however, an explanation of the permeability of the cell wall, but is simply a general statement of one of the conditions which affect the power of the cells to take up salts actively from their solutions, this power being absent in the case of salts which furnish an insoluble calcium compound.

The Absorption of Fats.—We know from the researches of Munk, Lebedew, and others, that fats administered to an animal in excess of its diurnal requirements are stored up in the body in the form in which they are administered. Each cell of the body apparently possesses in itself the mechanism for the utilisation of these neutral fats, and for effecting in them the various changes involved in the successive stages of their disintegration and oxidation through which they are finally converted to CO_2 and water. The problem, therefore, of fat absorption is ultimately one of the simplest with which we have to deal, and involves merely the transference of the neutral fat of the food to the circulating fluids in such a form that it can be carried by them to the seat where it is required for the metabolism of the body, or where it may be stored up as a reserve substance.

A study of the contents of the alimentary canal after a fatty meal shows that this class of substance undergoes hydrolytic changes under the action of the digestive juices in exactly the same way as do the other classes of food-stuffs. The process of hydrolysis, by means of which the neutral fats are split into fatty acids and glycerin, commences already in the stomach.

It was shown by Marcet and Cash, and has been often confirmed since, that the gastric contents some hours after the ingestion of neutral fats contain a considerable proportion, up to 30 or 40 per cent., of free fatty acid. This splitting has been ascribed at various times either to the acid of the gastric juice or to a lipase secreted in the juice. The question can be regarded now as decided in favour of the latter alternative. Thus, it has been shown by Volhard, Kastle, Löwenhart and Falloise, that glycerin extracts of the mucous membrane of the fundus, as well as gastric juice obtained by Pawlow's method, rapidly hydrolyse neutral fats if these are subjected to the action of the ferment in a finely divided condition. The negative results, such as those of Contejean, were probably due to insufficient regard having been paid to the necessity for the fat to be in a fine state of subdivision. The gastric juice is not favourable to the spontaneous formation of an emulsion, so that if the emulsion be not already formed before mixing the fat with the gastric juice, so small a surface is subjected to the action of the lipase that practically no hydrolysis results. The suggestion by Boldireff, that the fat-splitting shown to occur in the stomach was really due to the regurgitation of bile and pancreatic juice through the pylorus, has been definitely negatived by the experiments of Falloise, who showed that a lipase could be extracted from the gastric mucous membrane even after total extirpation of the pancreas, and that lipolysis occurred in the stomach when this viscus was entirely shut off from the duodenum by obstruction of the pylorus. It is, however, in the intestine that the greatest amount of fat is hydrolysed. In this region there is a co-operation of pancreatic juice and bile, the addition of the latter fluid sufficing to increase the lipolytic action of the pancreatic juice five or six fold. It has been shown by Rockwood and Moore, and others, that this adjuvant action of the bile is due, not to a ferment, but to its content in bile salts and lecithin, the bile salts playing the chief rôle. A certain amount of lipolysis will occur also when neutral fat is introduced into a washed loop of the small intestine. Since, however, the

lipolytic power of filtered intestinal juice is minimal, it seems probable that the lipase, like so many others of the intestinal ferments, is chiefly intracellular, and that any fat splitting which occurs in the intestine is effected by the cells after rather than as a preliminary to the absorption of fat. The same process of hydrolysis will be effected by many species of the bacteria which make up the intestinal flora.

If, therefore, fat is not absorbed in this unchanged condition, the processes of digestion will finally result in the production of glycerin and fatty acids if the reaction be neutral or slightly acid. On the other hand, if the reaction of the gut be alkaline, the alkaline solution will combine with the fatty acids to produce soaps. Analyses of the contents of the gut after a fatty meal show that the greater proportion of the fats are present as a mixture of fatty acids and soaps, the amount of these substances, as compared with unchanged fat, increasing as we descend the gut. In our study of the absorption of fats we must therefore decide, in the first place, whether any fats are absorbed unchanged, and, in the second place, as to the mechanism by which the products of digestion, namely, fatty acids and soaps, make their way into and through the epithelium

Channels of Absorption.—In studying the absorption of fats the investigator is able to take advantage of the fact that the micro-chemical detection of this substance is usually very easy. Globules of fat or fatty acids containing any proportion of the unsaturated fatty acids have the property of reducing osmic acid, and, therefore, of being stained black by this reagent. Practically in all cases the fats which occur in the food or in the cells of the body contain oleic acid, or the glyceride of this acid, in association with palmitic or stearic acid, and, therefore, give the typical micro-chemical fat reactions.

In many cases it is useful to employ the specific stains for fats, such as Sudan red or alkanna red. It is important, however, to remember that the intensity of the fat reaction given by a cell is only an expression of the fat or fatty acid

contained in a free state in the cell, and is no criterion of the total amount of fat which may be extracted from the tissue. Thus, a normal heart muscle in section gives only a diffuse light brown coloration with osmic acid. After poisoning by phosphorus or by diphtheria toxin, every muscle cell may be found studded with minute black granules of fat. Chemical analysis shows, however, that the normal heart muscle contains as much fat as the degenerated muscle. Our micro-chemical methods will, therefore, throw no light on the amount of fat which is actually in combination with the cell protoplasm.

If an animal be examined a few hours after the administration of a meal rich in fats, the lymphatics of the intestine are seen to be distended with a milky fluid—chyle—and the same fluid is found filling the cisterna lymphatica magna and the thoracic duct. If the lymph from the thoracic duct be collected it will also be found to be milky, and chemical analysis shows us that the opacity is due to the presence of minute granules of neutral fat. Frank has shown that the fat in such chyle may amount to over 6 per cent., and that in a moderate sized dog 12 grammes of fat may be carried in the course of an hour from the intestine to the blood by this means. This great access of fat to the blood during fat absorption introduces corresponding changes in the blood. The plasma itself becomes milky, and if the blood be allowed to clot, the serum expressed from the clot is also milky. On standing, a layer of fat globules may rise to the surface of the serum in the same way as cream rises to the surface of milk. Fat is found in a free state in this finely divided condition in the blood plasma so long as fat is being absorbed in the intestine. During starvation it disappears entirely, the serum becoming perfectly clear. We thus see that part at any rate of the fat which is absorbed from the gut is carried thence by the lymphatic channels in the form of neutral fat to the blood stream, and in this fluid the fine globules of fat are carried to the various tissues of the body, gradually leaving the blood stream in a manner which at present has not been determined. Apparently, however, not all the fat which is

absorbed takes the path by way of the lymphatics and the thoracic duct. Ligature of the thoracic duct, if effective, certainly impedes the absorption of fat, but does not abolish it. If the thoracic duct lymph be collected during the absorption of a given quantity of fat from the intestine, not more than 60 per cent. of the fat which has disappeared from the gut can be recovered from the lymph. What happens to the remainder of the fat we do not know. Apparently it does not reach the blood in a finely divided condition. If the thoracic duct be ligatured, the percentage of fat in the blood rapidly falls to a certain minimum which remains constant, even during starvation. If, now, fat be administered, although a considerable proportion of it may be absorbed, the percentage of fat in the blood is not raised. If, therefore, the fat is absorbed directly into the blood it cannot be in the particulate condition, and it must be in such small quantities at a time that any fat absorbed is at once removed from the blood by the tissues through which this fluid flows. It is difficult to imagine that any large proportion of this lost fraction of the fat is absorbed into the blood stream in the form of soaps, since, as Munk has shown, soaps injected into the blood stream act as potent poisons and give rise, even in small doses, to a great fall of blood pressure, incoagulability of the blood, and a condition of coma. We must, therefore, leave out of account for the present the mechanism of absorption of this lost fraction, and endeavour to trace the course of the absorption of that part of the fat which makes its way into the lymphatics.

Histological Study of Fat Absorption.—Over the whole region of the gut where fat absorption is going on, the mucous membrane presents a whitish appearance, conditioned largely by the distension of the central lacteals of the villi with the milky chyle. Microscopic examination of a section of the villus during fat absorption shows that the absorption occurs, for the most part, through the epithelial cells. These are found closely packed with fat granules which, small at the beginning of the process of absorption, rapidly enlarge till they occupy the greater part

of the cell lying between the nucleus and the basilar striated border. Most observers are agreed that no fat globules are to be seen within the border itself. According to Altmann, the fat granules found in the cells during absorption are themselves produced by a transformation of fuchsinophile granules which are to be seen in the cell even during the fasting condition. At an early stage the small fat granules can be stained so as to show a distinct fuchsinophile envelope. Altmann interprets this appearance as showing that the epithelial cells take up the fat in a dissolved form, probably in a hydrolysed condition, and that then a process of synthesis occurs in the granules, leading to the formation of fat and their distension with this substance. When the process of absorption is in full swing, the meshes of the villus contain a number of free fat granules, and the leucocytes in these meshes are generally found also full of these granules. Considerable discussion has arisen as to the manner in which the fat granules leave the cells and effect an entrance into the central lacteal. It must be remembered that the fat granules in the chyle are extremely fine, and, therefore, are smaller than the coarse granules to be observed in the epithelial cells. According to Zawarykin and Schaefer, an important function in the transfer of the granules from epithelial cells to central lacteal was performed by the leucocytes. These were supposed to take up the fat granules extruded by the epithelial cells at the base of the villi, to wander into the central lacteal, where they broke down, furnishing in this way both the molecular bases of the chyle as well as its protein constituents. This view was strongly combated by Heidenhain, who pointed out that many of the granules staining darkly with osmic acid were not necessarily fat, and that the number of leucocytes within the villi were hardly sufficient to account for the amount of material observed. According to Reuter, the epithelial cells take up fat in a dissolved condition through the striated border, and deposit it as granules of neutral fat in the inner portion of the protoplasm. From here the fat is passed on by the protoplasm by

the side of the nucleus, and extruded in the form of very fine granules in the deeper parts of the inter-epithelial clefts, which thus function as true excretory channels for the epithelial cells. These cells thus act as excretory organs, the excretion, however, taking place in this direction, intestine to lymph space, instead of, as is the case with most glands, from lymph to free surface.

It is probable that the muscular mechanism of absorption described many years ago by Brücke plays an important part in the absorption of fats, but it is difficult to furnish any experimental proof of the manner in which this mechanism works. From the muscularis mucosæ fine unstriated muscle fibres run up through all parts of the villus to be attached partly to the basement membrane of the epithelium, partly to the endothelial wall bounding the central lacteal. This vessel, as was shown by Mall, runs down into a superficial plexus of lymphatics in the mucous membrane which is devoid of valves, and the superficial plexus communicates by vertical branches with a deep plexus in the sub-mucosa richly provided with valves. Any rise of pressure in the lymphatics of the mucous membrane will cause a passage of fluid into the deep plexus, whence reflux is impossible by reason of the valves. Thus, repeated contractions of the muscle fibres described by Brücke would tend to empty the villus spaces into the central lacteal, and this in its turn into the sub-mucous plexus of lymphatics, so that we should have a true pumping action of the villus effecting the constant renewal of the lymph in its spaces, and a passage of this fluid laden with absorbed fat particles into the valved lymphatics of the mesentery. Provided that the state of subdivision of the fat is sufficiently fine, we have no reason from our experience of the other endothelial membranes of the body to anticipate that the membrane surrounding the central lacteal would present any appreciable resistance to the entry of the chyle with its fat particles.

The Method in which the Epithelial Cells take up Fat from the Intestine.—For many years after the discovery by Bernard of the influence of the pancreatic juice on fat, the prevailing

view among physiologists was to the effect that this substance was taken up by the cells in a finely particulate form, the chief value of the pancreatic juice being by splitting a small fraction of the fat to aid in its emulsification, and therefore in its subdivision, into fine particles suitable for absorption. The idea that a large part or even the total fat absorbed might be taken up in a dissolved condition was first put forward by Kühne and Radziejewski in 1868, and during the last twenty years evidence in this direction has been accumulating with great rapidity, so that at the present time it seems doubtful whether any fat at all is absorbed except in such a dissolved condition. I may here briefly summarise the evidence on which this view is based.

(1) The presence of bile in the intestine is essential for the proper absorption of fat. If this fluid be cut off from the gut either by the establishment of a biliary fistula or in consequence of obstruction of the bile ducts by a gall stone or by inflammatory swelling, the percentage of fat in the *fæces* at once rises, and the utilisation of this food-stuff drops from about 98 per cent. to perhaps 40 per cent., the loss by the *fæces* of fat being greater the larger the proportion of this substance there is in the food. This large undigested residue of fat hinders also the absorption of the other food-stuffs by coating them with an insoluble layer, so that nutrition, as a whole, may suffer considerably. On the other hand, if a fat-free diet be adopted, the utilisation of the food-stuffs is almost as complete in the absence of bile as in the normal animal. The important part played by bile in conjunction with the pancreatic juice in the absorption of fat was also shown by Dastre. In the rabbit, the white mesenteric lacteals denoting the absorption of fat are only seen below the point at which the pancreatic duct enters the duodenum, *i.e.*, about 20 centimetres below the entry of the bile duct. If the latter duct be transplanted so as to open into the small intestine a considerable distance below the point of entry of the pancreatic duct, fat is only found to be present in the lymphatics leading to the intestine below the

transplanted bile duct. It was shown by Schiff by means of his amphibolic fistula, and confirmed by Dastre, that the bile which is poured into the gut undergoes a circulation, being reabsorbed from the lower parts of the digestive tube, carried to the liver by the portal vein, and re-secreted in the bile. This fact, together with the known solvent properties of bile, suggest that the absorption of fat depends upon its solution in this fluid, the solution being then taken up by the cells. On arrival in the cells, fat is deposited while the bile salts pass on to be re-secreted, and to act as vehicle for another portion of fat. Bile does not dissolve neutral fats. On the other hand, it has a strong solvent action on fatty acids, on soaps, and even on such soaps as those of calcium, which are insoluble in water. The solubility of these substances in bile has been specially studied by Moore and Rockwood, and by Pflüger. Pflüger has shown that bile may dissolve as much as 19 per cent. of fatty acid, *i.e.*, a concentration of fatty acid greater than that which obtains in the case of any other food stuff in the gut. This solvent power is greatest in the case of oleic acid, and is very small in the case of pure stearic acid (less than 1 per cent.), but the solubility of stearic is largely increased if it be present, as is normally the case, in admixture with oleic acid. Moore has shown that this solvent action of bile is chiefly conditioned by the bile salts, but that the action of these salts is aided by the lecithin and cholesterin which are normally held in solution by them in the bile, a solution of lecithin and cholesterin in bile salts having a greater solvent power than a pure solution of the salts themselves.

(2) The absorption of fat from the gut may be interfered with in either of two ways, by shutting off the bile or by shutting off the pancreatic juice from the intestine. Fatty stools may be, therefore, the sign of disease either in the biliary passages or in the neighbourhood of the pancreatic duct. If the pancreas be excised, the absorption of fats is practically abolished. One may ascribe this result to the absence of the fat-splitting ferment of the pancreatic juice from the intestine,

but an analysis of the fæces shows that a very large proportion of the fat has been split into fatty acid or into soaps in the course of its passage from the alimentary canal. This lipolysis has, however, been carried out by the agency of micro-organisms which flourish especially in the lower segments of the gut, and it seems probable that the non-absorption of the fat is due to the fact that the lipolysis has occurred in the lower segments, *i.e.*, at a time when the greater part of the bile had been already re-absorbed into the portal circulation. This explanation is favoured by the fact that if fat be given to de-pancreatised animals in a finely divided form, such as cream or milk, a certain proportion of it is absorbed, and we have already seen that under these conditions a considerable degree of lipolysis may occur in the stomach itself, *i.e.*, at the very beginning of the alimentary canal, so that the fat would come in contact with the bile in the hydrolysed form.

The great difference between the results of ligature of the pancreatic ducts and extirpation of the pancreas suggests that in the latter case the effect is not simply due to the absence of the pancreatic juice from the intestine, but that the presence of this organ is in some way or other essential for the proper display of their absorbing functions by the epithelial cells of the intestinal mucosa. The defective utilisation of the food-stuffs extends, in fact, to the other two classes (animal proteins and carbohydrates).

I have thought that possibly the presence of pancreatic juice, apart altogether from its digestive effects, might facilitate or stimulate, in some way or other, the *absorbing* activity of the intestinal epithelium. Experiments failed, however, to bear out this hypothesis. Solutions, whether of salt, of carbohydrates, or of peptones, were absorbed with equal rapidity, whether or no pancreatic juice, bile, or gastric juice had been previously added to the solution to be tested.

(3) It was shown by Munk, as well as by Frank, that neutral fats made their appearance in the chyle as a result of the ingestion, either of soaps or of fatty acids. Since in this case a

synthesis of neutral fat must have taken place within the epithelial cells of the gut, there seems no reason to believe that a similar synthesis may not take place in the case of fat which had been taken in the neutral condition, and had been split in the gut as a result of the action of the pancreatic ferment.

(4) Substances which are physically almost identical with fats, *e.g.*, petroleum or paraffin, are not absorbed even when introduced into the intestine in the finest possible emulsion. Thus, if any of the well-known petroleum emulsions be administered for so-called therapeutic purposes, the whole of the petroleum present in the emulsion can be recovered from the faeces. Taking advantage of this non-absorbability, an ingenious experiment was contrived by Henriques and Hansen. Neutral fat was melted with a soft paraffin, and the resulting mixture beaten up into a fine emulsion. If the fats were taken up in a particulate form, the granules of mixed fat and paraffin ought to have been taken up together. There was no possibility of the fat being taken up in this form apart from the paraffin with which it was mixed. It was found, however, that the intestine rejected the paraffin, but took up the neutral fat. This result could only be explained by assuming that the fat in the particles had been dissolved out by the digestive juices, and that in this dissolved form they had been taken up by the mucosa. Whether any fat at all is taken up by the mucosa in a particulate condition, as has been imagined by Friedenthal, it is impossible to decide. The possibility is allowed by Munk, and denied by Pflüger. We are only justified in saying that in all probability the whole of the fat taken up from the intestine is in a dissolved condition, and that absorption of unaltered neutral fat, if it occurs at all, must do so only to a minimal degree.

We may sum up the processes involved in the digestion and absorption of fat as follows. Neutral fat is hydrolysed into fatty acid and glycerin under the action of the gastric juice, the pancreatic juice and the succus entericus, the effect of the gastric juice being, however, extremely limited unless the fat be presented to it in a finely divided condition. The lipolytic

action of the pancreatic juice and succus entericus is largely aided and increased five or six fold by the simultaneous presence of bile, which, in virtue of the bile salts, lecithin, and cholesterol it contains, enables the pancreatic juice to enter into close relation with the fat, dissolves the products of the activity of the ferment, and so enables it to attack renewed portions of the neutral fat. As the result of this lipolysis, there are formed glycerin, which is soluble in water, and fatty acids or soaps, according as the reaction of the medium is acid or alkaline. The alkaline soaps are soluble in water, the soaps of magnesium and calcium are soluble in bile, free fatty acids are soluble in bile acids. The fat is thus reduced to a condition in which it is soluble in the intestinal contents, whatever their reaction. In this state of solution its constituents are taken up by the cells of the intestinal mucosa. Within the cells the process of synthesis takes place, the soaps being split, and the fatty acids thus set free or absorbed being combined with glycerin with the elimination of water to form neutral fat, which appears as fine granules in the cell protoplasm. By an active process of excretion these granules are extruded in a somewhat more finely divided form into the intracellular clefts and into the spaces of the villus, whence by the contractions of the musculature of the villus they are forced with the lymph transuding from the capillary blood vessels into the central lacteal, and thence along the mesenteric lymphatics to the thoracic duct. This description would apply to probably 60 per cent. of the fat which is absorbed. It is probable that all the fat which is absorbed is taken up in a dissolved condition, but whether the remaining 40 per cent. enters the blood stream or is utilised and broken down in the tissues of the intestinal wall itself, we have no means of judging. Under normal circumstances the utilisation of fat is almost complete. By the time the intestinal contents have arrived at the lower end of the ileum, 95 per cent. of the fats have been absorbed. Removal of the whole large intestine was found by Vaughan Harley not to affect fat absorption.

In an important paper recently published by Rossi, considerable doubt is thrown on the absorption of soaps, as such, from the intestine. It has already been mentioned that soaps in contact with surviving intestinal epithelium undergo hydrolysis with the formation of free fatty acid (Moore, Rossi, Frank). Rossi has shown that when the epithelium of the small intestine is placed in contact with olive oil, the cells take up the acid, which collects in the form of fine granules, almost entirely confined to the part of the cell immediately underlying the striated basilar border. The same phenomenon is to be observed when thin sections of formalin-hardened mucous membrane is treated with oleic acid. Rossi ascribes this taking up of the fatty acid to the presence in the cells of some substance, removable by ether and xylol, which has a special avidity or solubility for fatty acids.

The entry of the fatty acid is much facilitated by the presence of bile. Neutral fats have no power of penetration. If the cells are treated with sodium oleate they load themselves with granules of the free fatty acid. The epithelium of the stomach and oesophagus has no power of taking up fatty acids.

Absorption of the Lecithins.—Experiments by various authors on the effects of feeding with lecithin, in which a marked acceleration of the rate of growth was obtained in young animals by increasing the amount of this substance in the diet, suggest that the lecithins must form an important constituent of the food. By their structure the lecithins must be classed with the fats, containing as they do one or more fatty acids, glycerin, phosphoric acid, and choline. The fats of these substances in the intestine cannot, however, be regarded as definitely established. It is evident that under the action of ferments or chemical agents a splitting of the molecule may occur between the glycerin and the fatty acid, between the glycerophosphate of choline and the fatty acid, or between the phosphoric acid and choline and the glyceride of the fatty acid, and, finally, choline may itself be split off. In considering their possible fate

in the intestine, it is important to take into account not only the ferments present in the digestive juices, but also the reaction of these juices, and it is possible that some of the results obtained by the action of pancreatic juice on lecithin were due rather to the alkalinity of this juice than to the presence of lipase in it. According to Bokay, no traces of lecithin were found in the fæces after a diet rich in this substance, and the same results were obtained by Haserbroek. The fate of lecithin has recently been the subject of investigation by various physiologists. Stassano and Billon investigated the action of pancreatic juice, which had been activated by the addition of enterokinase, on a lecithin emulsion. According to these authors, if the lecithin is fresh, no hydrolysis takes place. On the other hand, if the lecithin has been prepared for some time and has been exposed to air and moisture, it rapidly undergoes hydrolysis under the action of pancreatic juice whether enterokinase be present or not. They conclude, therefore, that lecithin as ordinarily taken in food probably undergoes no change in the alimentary canal. In confirmation of this conclusion they quote the results of an experiment on large dogs of 20 to 40 kilos which received, together with a meal, 10 to 15 grammes of pure lecithin. On collecting the thoracic duct lymph some hours (5 to 9) after the meal, they were able to separate a large quantity of lecithin from the lymph. On the other hand, if the lecithin be given in conjunction with protein, i.e., in the form in which it occurs in egg yolk, a large amount of hydrolysis occurs even under the action of pancreatic juice, fatty acid being set free. Similar results were arrived at by Sloutzoff. Other authors, however, have obtained a liberation of free fatty acid by the action of pancreatic juice upon freshly prepared lecithin, and it is evident that further experiments on both the digestion and the absorption of lecithin are necessary before we can pronounce a definite opinion upon this subject.

Absorption of Protein.—In very few departments of physiology has there been so great a revolution in our ideas as in that

affecting the question of protein absorption, especially as to the form in which it is absorbed from the alimentary canal, and its fate after absorption. As to the channel by which it obtains entry into the circulation, practical agreement reigns that it is absorbed by the blood vessels. Almost every physiologist who has occupied himself with the investigation of the lymph flow from the thoracic duct has been impressed by the fact that the variations in the amount of lymph to be obtained in this way bear no relation to the condition of the animal as regards the state of digestion. Nor do we find any appreciable increase in the amount of lymph flow or in the amount of proteins contained in this lymph during digestion. The small increase observed by Asher and Barbera would be sufficiently accounted for by the increased blood supply to the intestines during digestion, and is insufficient to account for the absorption of any appreciable quantity of the protein which is being taken up from the alimentary canal. Moreover, it was shown by Schmidt Mülheim that the absorption of proteins was not interfered with as the result of ligature of the thoracic duct, and that after this duct had been ligatured, the ingestion of proteins was followed at the usual interval by the increased output of urea which is the invariable concomitant of protein absorption and assimilation. We must therefore conclude that the products of protein digestion are taken up by the epithelial cells and passed on by these into the blood vessels. During the absorption of a protein meal changes have been described by various observers in the structures of the villus. In nearly every case there is marked increase in the number of mitotic figures in the epithelium lining the follicles of Lieberkühn. According to Hofmeister there is during absorption an increase in the number of leucocytes in the villi, and this observer ascribed an important function to these leucocytes in the absorption of protein. Heidenhain showed that this increase of leucocytes was not constant in all animals, and bore no relation to the amount of absorption that was taking place, and was quite inadequate to account for the total absorption that was being carried on.

On the other hand, several observers have described changes in the epithelium as the result of protein digestion. According to Reuter the epithelial cells become swollen, their protoplasm stains less deeply, and at their basal ends the cells' limits disappear, the protoplasm being apparently distended with hyaline coagulable material. Reuter regards this appearance as a direct expression of the taking up of proteins in a dissolved crystalline form and their conversion near the bases of the cells into coagulable proteins; but further evidence on this subject is necessary before we can attach much importance to such an interpretation of the appearances observed.

The whole problem of absorption of proteins, both as to its nature and mechanism, is bound up with the question as to the form in which the proteins are absorbed, and the form in which they obtain entrance into the blood stream, and it is these questions which we must now consider. Under the influence of the gastric juice the proteins of the food are resolved during their stay in the stomach into albumoses and peptones. In the small intestine the process of hydration is carried further, the trypsin of the pancreatic juice carrying the proteins through the stage of secondary albumoses and peptones, and converting them into a mixture of amino-acids and polypeptides. The same end-products result from the action of the erepsin of the intestinal wall on the albumoses and peptones produced by gastric digestion. The digestive juices finally reduce the proteins, therefore, to a mixture of the following substances: glycine, alanine, serine, leucine, glutamic and aspartic acids, tyrosine, phenyl-alanine, tryptophane, lysine, histidine, arginine, and probably a few other amino-acids in small quantities. In addition to these substances there is probably always a certain remainder of polypeptides, consisting of two or three of the amino-acids associated together, which do not undergo further disintegration under the action of the intestinal ferments. The final products, however, give no biuret test. The first question we have to decide is to what extent the proteins are reduced to their ultimate

hydration products before absorption. Must they undergo complete hydration as a necessary preliminary to absorption, or may they be taken up without undergoing any action at all, or in the stage of partial hydration as albumoses and peptones?

The Absorption of Unchanged Protein.—We have obtained evidence that protein may be absorbed by the small intestine without having undergone any hydration whatsoever. The absorption of serum protein has been discussed already in dealing with the mechanism of absorption of salt solutions from the gut. In a series of experiments made by Friedlander the absorptions of various proteins were compared after their introduction into loops of the small intestine which had been washed free from ferment. During a period of three hours this author found that 21 per cent. of the proteins of egg white or of blood serum were absorbed. During the same period, of alkaline albumen which had been introduced into the loops, 69 per cent. was absorbed. On the other hand, when syntonin and casein were introduced into the intestine, no absorption whatever was observed. Similar experiments have been carried out on the large intestine, and there can be no doubt that unchanged coagulable protein may be absorbed from the alimentary canal in the absence of digestive ferments. As to the condition in which such unchanged protein reaches the blood stream, our knowledge is still imperfect. Foreign proteins, such as egg albumen, or the serum of other species introduced into the blood stream, may cause poisonous effects, and may give rise to albuminuria, to lowering of blood-pressure, or to alteration of the coagulability of the blood. If injected in small quantities they excite, as a reaction on the part of the organism, the production in the blood serum of a precipitin, and the presence of the precipitin may be looked upon, therefore, as a test by which we may decide whether these proteins have passed through the intestinal wall unchanged. In most cases it is found that however abundant the amount of protein administered in the soluble form, none of it appears in the urine, nor is any precipitin formation aroused. Ascoli has, however, observed such

events occasionally to follow the administration of large doses of egg white, and it has been shown that there is a large difference in the behaviour of animals to the introduction of soluble protein into their alimentary canal, according as they are new born, or are more than a few days old. It seems that during the first few days of life the cellular lining of the alimentary canal is permeable to foreign proteins, whereas later on any protein which is taken up unchanged from the gut does not arrive in the same unchanged condition in the blood stream.

The absorption, however, of unchanged proteins can play but a small part in the assimilation of protein as a whole. Animals very rarely take coagulable proteins in a condition in which they will arrive at the small intestine in a state of solution unchanged. Even in the carnivora the living tissues taken into the stomach will undergo coagulation by the acid, and will then be dissolved by the gastric juice. In man, practically all the proteins of the food are either insoluble or are rendered insoluble by the process of cooking. For absorption to take place it is therefore necessary that this insoluble or coagulated protein should be brought into solution, and this process is accomplished, together with hydration, by means of the ferments of the gastric and pancreatic juices. This process of solution has long been regarded as the chief object of the digestive ferments. Although both Kühne and Schmidt Mülheim were aware of the production of amino-acids, such as leucin and tyrosin, as the result of digestion, they regarded their production as evidence of a waste of material. Albumoses and peptones are soluble, diffusible, and rapidly absorbed from the alimentary canal, and there is no doubt that a large proportion of the products of protein digestion are taken up by the absorbing membrane in this form. For many years the physiologists were occupied with the problem as to the fate of these peptones and albumoses after their entrance into the mucous membrane. They do not pass as such into the blood. The injection of small quantities of albumose and peptone into the blood gives rise to

the excretion of these substances by the kidneys; injection of larger quantities has pronounced poisonous effects, which were first studied by Schmidt Mülheim and Fano. If samples of blood be taken, either from the portal vein or from the general circulation after a heavy protein meal, no trace either of albumose or of peptone is to be found in the blood. The observations of Hofmeister and others to the contrary depend on the fact that these observers employed a method for the separation of coagulable protein as an antecedent to the testing for albumoses which was in itself capable of producing small traces of these substances. Hofmeister showed that during the absorption of a protein meal the mucous membrane either of the stomach or of the intestine, if rapidly killed by plunging into boiling water directly it was taken from the animal, always contained a considerable amount of peptone, and similar observations were made by Neumeister. If, however, the mucous membrane was kept warm for half an hour after removal from the body, the peptone disappeared. Salvioli, under Ludwig's guidance, introduced peptone into a loop of gut which was kept alive by passing defibrinated blood through its vessels. At the end of some hours the loop was found to contain a certain amount of coagulable protein, but no trace of peptone, nor was any trace of the latter substance found in the blood which had been passed through the vessels. These observations were interpreted as pointing to a regeneration in the intestinal wall of coagulable protein from the albumose and peptone taken up from the gut, and opinions were divided whether the most important part of this regeneration was to be ascribed to the leucocytes of the villi (Hofmeister), or to the epithelial cells of the mucous membrane itself.

It is evident that such a conclusion was not justified by the experiments. All that these experiments showed was that the albumoses and peptones disappeared, *i.e.*, were converted into something which did not give the biuret test. The discovery of the ferment, erepsin, by Cohnheim, led this observer to repeat the experiments of Hofmeister and Neumeister with a

view to testing the conclusions drawn by these physiologists. Cohnheim found that, although it was perfectly true that albumose and peptone disappeared when intestinal mucous membrane and peptone were placed together in the presence of either blood or of Ringer's fluid, this disappearance was due, not to a regeneration of coagulable protein, but to the fact that the erepsin of the mucous membrane carried the process of hydrolysis a step further, converting the albumoses and peptones into the ultimate crystalline products of protein hydrolysis. Similar observations were made by Kutscher and Seemann, who showed that at any time after a protein meal these end-products, especially leucin, tyrosin, lysin, and arginin, were to be found in the contents of the small intestine. A repetition of Salvioli's experiment by Cathcart and Leathes deprived this also of much of its significance. It was found that the artificial circulation, although sufficient to maintain the activity of the muscular wall of the intestine, as evidenced by the peristaltic movements, was insufficient to keep the mucous membrane alive. After one hour's experiment the loop contained a mass of epithelial cells mixed with the products of the action of erepsin on the introduced peptone solution. In no case was there any diminution in the amount of nitrogen in the form of uncoagulated material, *i.e.*, there was no formation of coagulable protein, while the processes of absorption had been brought by the desquamation entirely to a standstill.

These additional experiments caused a complete revolution in the attitude of physiologists towards the problem of protein absorption. All this evidence went to show that protein, however introduced, whether as coagulated protein or as albumose and peptone, underwent complete hydrolysis either in the gut or in the wall of the gut before entering the blood stream. If this were the case, it should be possible to feed an animal on a diet in which the necessary protein had been replaced by the corresponding amount of ultimate products of protein hydrolysis, *i.e.*, by a mixture which would give no biuret reaction. Such a possibility had previously been negatived on theoretical grounds

by Kühne and by Bunge. It was thought by these observers either that the animal body lacked the power of synthesis of proteins from these crystalline products (hydration products), or that any complete hydration occurring in the intestine would involve such a loss of energy to the body as to be unteleological. Neither of these theoretical objections are justified in fact. We know from the researches of Fischer and others that although the different proteins in our food present a marvellous qualitative similitude, in that all of them yield on hydrolysis the same kinds of amino-acids, there is an enormous difference in the relative amounts of these amino-acids contained in different proteins. Thus, in gelatin, glycin is contained in considerable quantities, but is absent in many of the other proteins. Caseinogen is distinguished by the large amount of leucin that it yields, while gliadin, the chief protein of wheat flour, contains very large amounts of glutamic acid. It is difficult to imagine how, for instance, muscle protein could be formed from wheat protein, a process continually occurring in the growing animal, unless we assumed that the protein molecule is first entirely taken to pieces, and that its constituent molecules are then selected by the growing cells of the body and built up in the order and proportions which are characteristic of muscle protein. Moreover, when we measure the amount of energy change involved in the hydrolysis of the proteins, we find it is relatively small. There is not a loss of 5 per cent. of the total energy available, *i.e.*, the heat of combustion of the products of pancreatic digestion would differ from that of the original protein submitted to digestion by less than 5 per cent. The energy of the protein as evolved in the body lies not in the coupling of the amino-acids with one another, or indeed in the coupling of the nitrogen to the carbon, but like that of the other food-stuffs, in the carbon itself, and is derived from the combustion of the carbon of the molecule under the influence of the oxidising processes of the body into carbon dioxide. The experimental decision of this question was first attempted by O. Loewi, who found that it was possible to keep a dog

in a state of nitrogenous equilibrium on a diet containing fat, starch, and a pancreatic digest of protein which contained no substances which would give the biuret test. These results have been confirmed for carnivora by Henderson, by Luthje, by Abderhalden and Rona, and by Henriques and Hansen. According to Abderhalden, it is possible to keep an animal alive when the nitrogen in his food is represented entirely by the end-products of pancreatic digestion. The same result cannot be attained by the administration of the products of acid hydrolysis of protein, but this may be due either to the racemisation of the amino-acids under the action of the strong acid, or to the fact that the acid splits up certain polypeptide groupings which are still contained in the trypsin digest, and which possibly cannot be synthesised by the cells of the body.

We are justified, therefore, in concluding that while a certain small proportion of the proteins of the food may be absorbed unchanged, a much larger proportion is taken up as albumoses and peptones or as amino-acids. The proportion taken up in the albumose or peptone form is, however, rapidly changed in the mucous membrane itself into amino-acids, so that we may regard these substances as the form in which practically all the protein of the body is presented to the absorbing mechanisms of the alimentary canal for absorption and for passing on into the circulating fluids.

The Fate of the Amino-acids after Absorption by the Intestinal Epithelium.—During a condition of starvation, the normal protein requirements of the body, or rather of the active tissues, are met at the expense of the less active tissues. The protein, characteristic of any tissue, can be taken down, removed to another part of the body, and built up into the protein characteristic of some other active tissue. It is difficult to conceive that such a transference and transformation could occur in any other way than by a more or less thorough disintegration of the protein molecule at one place and its synthesis at the other, and we know from the researches of Hedin and others that every tissue contains intracellular ferments which are

capable of effecting the disintegration of the protein molecule, and are responsible for the autolytic degeneration of tissues after death. If, therefore, the normal interchange of protein between the tissues is accomplished, as we know it to be in plants, by the disintegration of the proteins into their constituent amino-acids and their subsequent re-integration, there is no *a priori* reason to believe that the blood carries the proteins from the alimentary canal to the tissues in any other form than that of amino-acids. The experimental proof of this conclusion meets with many difficulties. So great is the total volume of blood circulating through the vessels of the alimentary canal during the hours that the observation is taking place, that a considerable amount of amino-acids could be carried by this blood from the canal to the tissues without effecting a change in the composition of the fluid which is within our errors of analysis. The experimental investigation of this point has been attempted by Kutscher and Seemann, and by Cathcart and Leathes. The former observers analysed the portal blood during active protein digestion after cutting out by ligature the circulation from all parts of the body except the heart, lungs, liver and alimentary canal. They were unable to detect any increase in the amount of amino-acids in the blood. Cathcart and Leathes investigated the content of the blood in soluble, *i.e.*, non-protein nitrogen, in normal animals and in anaesthetised animals in whom large quantities of peptone solution had been introduced into the small intestine, and found a distinct increase in the latter case. In this experiment the rates of absorption of the products of protein digestion were increased much above their normal value, whereas in the experiments of Kutscher and Seemann the rate of absorption in consequence of the operative procedure was probably less than would obtain in the normal animal after such a protein meal. The evidence, therefore, so far as it goes, is in favour of part, at any rate, of the protein being carried by the blood to the tissues in the form of amino-acids.

The negative results obtained by Kutscher and Seemann suggested to these observers that possibly some process of inte-

gration might occur in the mucous membrane of the alimentary canal itself, and they were strengthened in this conclusion by the fact that although no amino-acids could be extracted from the intestinal wall, they were able, after treating the mucous membrane with acid, to extract leucin, a fact suggesting that the leucin had been combined in some ester-like compound with some other constituent of the mucous membrane. Abderhalden is apparently inclined to believe that there is an actual regeneration of the protein in the mucous membrane, a formation from the amino-acids of blood protein, either serum albumen or serum globulin, and that this blood protein acts as a common protein food for all the different cells of the body. It is difficult to bring any experimental proof for this view. It is, however, practically certain that a considerable proportion of the protein and of its crystalline products is broken up still further in the mucous membrane. All observers who have investigated the point concur in the statement that the portal blood contains more ammonia than does the blood of the arterial system, and it seems probable that, as suggested by Leathes and Folin, a large proportion of the amino-acids undergo de-aminisation in the wall of the gut, so that the products that are actually absorbed are ammonia and a fatty acid or its oxy-derivative. The ammonia passes through the liver and is at once converted into urea, so that the postprandial rise in urea excretion is due to this immediate de-aminisation of the ingested protein. What happens to the non-nitrogenous moiety of the protein radicle we do not know. It is apparently oxidised fairly rapidly, since excessive protein ingestion does not give rise to any formation of fat, but produces in every case an increase in the respiratory exchanges and in the output of CO_2 . At the present time it is impossible to decide with any certainty as to which of these views of the fate of the ingested protein is correct. It is possible that all three processes may take place, viz., that a proportion of the protein may be built up in the cells lining the alimentary canal to form blood protein, so that this organ would have to be regarded as an important blood-

forming organ, and that another portion representing the amount required to replace the tissue waste of the body, is absorbed into the blood stream as amino-acids, in which form it is carried to the tissues and re-integrated into the protein characteristic of each tissue. A third portion, probably the major part of the protein, does not reach the tissues at all as a nitrogenous compound, but undergoes de-aminisation in the intestinal wall, the nitrogen being rapidly carried to the liver and converted into urea, and then excreted by the kidneys, while the non-nitrogenous moiety is carried to the tissues to which it serves as a ready and important source of energy. Further investigation on all these points is, however, urgently required.

The Absorption of Carbo-Hydrates.—As a result of the action of the various digestive juices, all the carbohydrate constituents of the normal diet of man are reduced to the state of monosaccharides. The absorption of these digestive products may take place at any part of the alimentary canal, the greatest part in the process of absorption being taken by the small intestine. By the time that the food has arrived at the ileo-cæcal valve practically the whole of the carbohydrate constituents of the food have been absorbed. So far as concerns the channels of absorption, all experimenters are agreed that the carbohydrates pass into the body by way of the vessels of the portal system. The lymph from the thoracic duct contains no more sugar than does the arterial blood taken at the same time, whereas several observers have obtained an increased percentage of sugar in the portal blood during the absorption of a big carbohydrate meal.

Of the carbohydrates of the food, some, like starch, dextrin, glycogen, are colloidal and indiffusible; others, such as the disaccharides, cane sugar, milk sugar, and maltose, are soluble and diffusible, and the products of the action of digestive ferments on these two classes, namely, the monosaccharides, mannose, fructose, glucose, galactose, are also soluble and diffusible. The problem as to the mechanism involved in the passage of these substances across the intestinal wall into the blood vessels

has been dealt with already in treating of the absorption of water and salts. The most striking fact is the relative impermeability of the intestinal wall to the disaccharides as compared with the monosaccharides. The intestinal wall is apparently only able to take up in any quantity such sugars as can be utilised by the cells of the organism. For this purpose the disaccharides are useless; cane sugar or lactose introduced into the blood vessels or subcutaneously are excreted quantitatively in the urine, and, as might be expected, they do not increase in any way the glycogen of the liver. When maltose is injected in the same manner, a certain proportion of it is utilised owing to the fact that the blood and fluids of the body contain a ferment, maltase, capable of converting the disaccharide into the monosaccharide, glucose. The absorption of these disaccharides occurs, therefore, much more slowly from the intestine than does the absorption of monosaccharides, the process of absorption being always preceded by and waiting for the process of hydrolysis. Thus, huge doses of cane sugar may be taken without causing the appearance of cane sugar in the blood or urine. It has been found that sugar does not appear in the urine until as much as 320 grms. of cane sugar have been ingested, whereas any quantity of glucose over 100 grms. gives rise to glycosuria. Lactose is absorbed still more slowly, and I have found that in animals whose intestine is free from the ferment, lactase, lactose is not absorbed; large doses of lactose in such animals, therefore, give rise to diarrhoea. The same fact is illustrated by an experiment of Waymouth Reid. This observer, after the injection of maltose into a loop of normal intestine, found only maltose in the fluid taken from the loop after some time. After, however, the epithelium of the loop had been destroyed by any means, the contents of the loop after half an hour contained large quantities of glucose. In the first case, the absorption of glucose had gone on as rapidly as its formation under the influence of the maltase of the intestinal wall, so that only the unacted-on maltose remained in the gut. In the second case, the process of absorption was brought to an end

by the destruction of the epithelium, and maltose, together with its products of digestion, glucose, remained in the gut. The monosaccharides are not all absorbed at the same rate. Nagano, experimenting on the small intestine in dogs, found that dextrose and galactose were absorbed more rapidly than fructose and mannose, while the pentoses, xylose and arabinose, passed in still more slowly.

The behaviour of the intestinal wall to the non-assimilable sugars of artificial origin has not yet been sufficiently investigated. It would be interesting to inquire whether the rate of absorption of the ordinary sugars was in any way determined by their stereomeric configuration; whether, for instance, glucose would be absorbed as rapidly as the ordinary glucose. Experiments carried out by Dakin on the absorption of the tartrates failed to give any indication of such polarity in the absorbing function of the cells. A difference might, however, be brought out on presenting the cells with substances such as artificial sugars, which are incapable of being utilised by the cells of the body as a whole.

PART VI.

A.—FUNCTIONS OF THE LARGE INTESTINE.

In no part of the alimentary canal do we meet with wider differences in animals than in the large intestine. These differences depend not on the class to which the animal belongs, but on the nature of its food. It is true that in the small intestine there are variations in length according to the digestibility of the food taken. Thus, in the cat the small intestine is three times as long as the body; in the dog, four to six times; in the pig, fourteen times; whereas in the purely herbivorous animals, such as the goat and sheep, the small intestine is twenty-seven times as long as the body. Man occupies an

intermediary position corresponding to his mixed diet, the small intestine being about seven times as long as the distance between the occiput and the tip of the sacrum. The great development of the large intestine, and especially of the cæcum, in herbivorous animals, shows that in these animals important processes of digestion must occur in this part of the gut. In such animals a very large proportion of the food-stuffs, namely, the proteins and carbohydrates, are shut up within the cellulose walls of vegetable cells. Since none of the higher vertebrata have the power of producing a cellulose digesting ferment in their alimentary canal, these food-stuffs would be lost to the body were not some other means provided for the solution of the cellulose. This means is by the agency of bacteria. The mass of vegetable matter which accumulates in the cæcum is a rich breeding-ground for bacteria, and especially for the bacteria which feed upon cellulose. These bacteria dissolve the cellulose, and ferment it with the production of fatty acids, methane, carbon dioxide and hydrogen. By this means the contents of the vegetable cells are set free and can be absorbed by the walls of the large intestine.

We thus see that the importance of the large intestine is in direct ratio to the digestibility of the food. In primitive man, and in all nations living in low conditions and dependent for their nutriment on coarse vegetable foods, it is probable that the large intestine is of considerable importance. In civilised man, however, who chooses out the most digestible food-stuffs, prepares them for the processes of digestion by grinding, cooking and separation of all the harder parts, the large intestine can have very little value as an organ of digestion. The processes both of digestion and absorption are practically complete by the time that the food has arrived at the lower end of the small intestine in a dog fed on what we may term a civilised diet; and observations on intestinal fistulæ in man situated at the lower end of the ileum lead to the same conclusion.

The glands in the large intestine are almost entirely occupied with mucus-secreting cells. Any fluid formed in the large

intestine consists chiefly of mucus, and is free from ferments which would act on the food-stuffs. We must regard the mucin as a means of protection against the bacteria which swarm in this part of the alimentary canal. Mucin is known to play a similar protective part in many fishes, where it is produced as a secretion from the glands of the skin. Thus, any digestion which takes place in the large intestine is due to bacteria, and in man this digestion is unnecessary and, in many cases, harmful.

On the other hand, the large intestine probably plays an important part as an organ of excretion. Thus, calcium salts injected subcutaneously may be excreted in large part in this portion of the gut. Whether it is excreted with the faeces or with the urine depends on the supply of acid available. Thus, on a vegetable diet calcium will appear chiefly in the faeces; on an animal diet a large proportion of it will be excreted by the kidneys. The same holds good for magnesium. Iron which, as we have seen, is absorbed practically entirely from the duodenum, is re-excreted into the large intestine, only small traces of it making their appearance in the urine. Mercury, also, whether absorbed from the alimentary canal or from a wound surface, is mainly excreted in the large intestine, and it is this distribution of mercury which probably accounts for the production of an ulcerated condition of the colon in cases of poisoning by this metal. When bismuth is taken by the mouth we get a blackening of the mucous membrane of the large intestine which is strictly limited above by the ileo-cæcal valve. The same blackening occurs when bismuth is given subcutaneously, showing that it is determined by the excretion of the bismuth by the mucous membrane of the large gut. So far as civilised man is concerned, we must, therefore, regard the large intestine as an organ not so much of digestion as of excretion. So far as the food is concerned, it serves merely as a reservoir for the faeces and a place where a certain proportion of water can be absorbed from the faeces.

B.—MOVEMENTS OF THE LARGE INTESTINE.

In consequence of the occasional peristaltic contraction of the small intestine, accompanied by relaxation of the ileo-colic sphincter, the contents of the ileum, consisting of debris of cells, of small traces of unabsorbed food, and of the remains of the digestive juices, are gradually transferred into the large intestine. In man these contents are semi-fluid and fairly large in bulk, and probably fill the ascending and part of the transverse colon. This part of the intestine is well supplied with nerves derived either directly or through the sympathetic system from the spinal cord. The action of these nerves has been especially investigated by Langley and Anderson. It also possesses a local nervous system similar to the plexuses of Auerbach and Meissner in the small intestine. I have investigated the functions of this local nervous system, especially in the dog. In order to avoid disturbing influences from the central nervous system, we may expose the large intestine in warm normal saline, after having previously severed all connections between it and the central nervous system. Under such conditions in the dog the colon is generally seen to be in a state of moderate constriction. Spontaneous descending contractions of the gut are rarely noticeable on simple inspection. If the small intestine be in an active condition, peristaltic contractions are occasionally seen which pass down the ileum and, if its connection with the colon be not destroyed, pass over the ileo-cæcal junction to the colon. Such a peristaltic wave may be produced at will by the insertion of a bolus of cotton-wool and soft soap into the small intestine. The bolus is driven into the colon and down it for some distance, but the peristaltic wave, as a rule, dies away at about the middle of the colon or the beginning of its descending part, and if several boluses be inserted one after the other, they all tend to accumulate about this part of the colon. In some cases, with an active colon, the accumulation at this part excites a peristaltic wave which drives the accumulated mass down the whole of the descending colon and out of the lower orifice.

On inserting the recording balloon into the colon, we find, as a rule, that this viscus is the seat of rhythmic contractions, which, starting above the balloon, appear to travel downwards. These contractions are quite different in character from the rhythmic beat of the small intestine; they are much larger and of less frequency, and each contraction may last from ten to forty seconds. Superposed on these large contractions smaller ones may generally be seen, not very regular, but having an individual duration of two to four seconds. I have not been able to decide definitely whether there is any fundamental difference in the mode of origin of these two classes of contractions, whether, for example, the large contractions are neurogenic, and the small superposed waves myogenic, in origin.

One meets, however, with extreme variations in the activity of the muscular wall of the colon. In some cases it enters into a state of tonic contraction, presenting no mark of rhythmic action: in other cases (more rarely) it is perfectly inactive and in a position of complete relaxation.

As in the small intestine of the dog, so in the large, it is extremely easy, after complete destruction of its nervous connections, to evoke a descending inhibition. A stimulus, such as a pinch, applied to any part of the colon, or even to the lower part of the ileum, produces at once complete inhibition of the whole of the colon below the stimulated point.

The same inhibitory effect occurs below a descending peristaltic wave, so that the effect of a series of peristaltic waves dying away, as they generally do, at the beginning of the descending part of the colon, must be to distend more and more this part of the colon. We have already seen that in a particularly active gut this accumulation may result in the production of the peristaltic wave in the descending colon, and an emptying of this portion of the gut. It is probable, however, that in the intact animal the accumulation in this situation excites motor discharges through the lumbar spinal cord, and that the emptying of this portion of the gut is under the control of the central nervous system. In no case after complete enerva-

tion of the gut is an ascending inhibition ever observed as the result of local stimulation.

As we should expect from the greater sluggishness of the large as compared with the small intestine, it is much more difficult in the former to evoke evidence of an ascending excitatory change as the result of local stimulation. On many occasions I have been unable to obtain any contraction by stimulation of the gut immediately below the recording balloon, the descending inhibition due to the presence of the balloon being more than sufficient to counteract the excitatory effects of the local stimulation. In some cases, however, especially if the balloon be in the upper region of the colon, pinching the intestine half an inch below the balloon may evoke contractions over the balloon.

In the same region of the gut it is generally possible, by the insertion of a bolus moistened with soft soap, to assure oneself of the existence of an ascending excitation from the stimulated point. A band of constriction appears in the gut above the bolus, and gradually spreads down towards the middle of the colon, driving the bolus in front of it.

On the dog, however, we can only investigate part of the phenomena presented by the more highly developed large intestine of the cat or man himself. Elliott has shown that, if one considers a number of different animals, one must divide the large intestine into four parts according to their functions, viz., the cæcum, and the proximal, intermediate and distal portions of the colon. Of these, the dog possesses practically only the distal colon. We may take Elliott's account of the movements as they probably occur in man. They agree very closely with those observed by Cannon under normal circumstances in the cat, by means of the Röntgen rays. The food, as it passes from the ileum, first fills up the proximal column. The effect of this distension is to cause a contraction of the muscular wall at the junction between the ascending and transverse colon. This contraction travels slowly over the tube in a backward direction towards the cæcum, and is quickly

succeeded by another, so that the colon may present at the same time several of these advancing waves. These waves are spoken of as anti-peristaltic; but, as they do not involve also an advancing wave of inhibition, they must not be regarded as representing the exact antithesis of a peristaltic wave, as I have defined it. The effect of these waves is to force the food up into the cæcum, regurgitation into the ileum being prevented partly by the obliquity of the opening, partly by the tonic contraction of the ileo-colic sphincter. As the whole of the contents cannot escape into the cæcum, a certain portion will slip back in the axis of the tube, so that these movements have the same effect as the similar contractions in the pyloric end of the stomach, causing a thorough churning up of the contents and their close contact with the intestinal wall. The movements are rendered still more effective by the sacculation of the walls of this part of the large intestine. The distension of the cæcum caused by this anti-peristalsis excites occasionally a true co-ordinated peristaltic wave, which, starting in the cæcum, drives the food down the intestine into the transverse part. These waves die away before they reach the end of the colon, and the food is driven back again by waves of anti-peristalsis. Occasionally more food escapes through the ileo-colic sphincter from the ileum, so that the whole ascending and transverse colon may be filled with the mass undergoing a constant kneading and mixing process. The result of this process is the absorption of the greater part of the water of the intestinal contents, as well as of any nutrient material, and the drier part of the intestinal mass collects towards the splenic flexure, where it may be separated by transverse waves of constriction from the more fluid parts which are being driven to and fro in the proximal and intermediate portions. By means of occasional peristaltic waves these hard masses are driven into the distal part of the colon. The distal colon must be regarded as a place for the storage of the fæces, and as the organ of defæcation. In the transverse colon, in the descending and ilio-colon, the anti-peristaltic movements and consequent churning

of the contents are probably slight. These, therefore, represent the intermediate colon with propulsive peristalsis as its chief activity. The descending colon is never distended, and Elliott therefore regarded it as a transferring segment of exaggerated irritability. The storage of the waste matter takes place chiefly in the sigmoid flexure. This with the rectum represents the distal portion of the colon. The distinguishing feature of the distal colon is its complete subordination to the spinal centres. It probably remains inactive until an increasing distension excites reflexly a complete evacuation of this portion of the gut. Since in this process of evacuation the extrinsic innervation of the large intestine is the most essential factor, it will be convenient to deal here with the action of the chief nerves passing to this part of the gut. The large intestine receives fibres from two sources, namely, from the upper lumbar nerves through the sympathetic system, and from the second and third sacral nerves by the pelvic visceral nerves or *nervi erigentes*. The sympathetic supply runs in the white *rami communicantes* to the main chain of sympathetic ganglia, and from here along communicating branches to the collection of ganglion cells situated round the beginning of the inferior mesenteric artery. Here they have their chief cell-station. From the ganglia a number of non-medullated fibres are given off which run along the inferior mesenteric artery to be distributed with the branches of this artery to the ascending transverse and descending colon. Two nerves, the hypogastric nerves, come off from the inferior mesenteric ganglion, and run down in the meso-rectum on each side of the rectum to take part in the formation of the hypogastric plexus. From this plexus fine fibres are given off to the terminal part of the large intestine. The *nervi erigentes* come off from the second and third sacral nerves, and run straight across to the neck of the bladder. Here they break up into a plexus forming part of the hypogastric plexus, and send fibres into the bladder as well as into the rectum. The branches of the latter apparently run in the wall of the gut as far as the ileo-colic

valve, since stimulation of the nerve causes effects which can be traced as far as the junction between the ileum and colon. The action of these nerves can be easily studied either by the graphic method or by inspection. It is important to keep the large intestine warm and moist, preferably immersed with the whole abdomen of the animal in warm normal saline solution. We may deal with the action of these two sets of nerves separately.

(a) *Sympathetic Nerve Supply*.—The effect of stimulating these nerves is to cause a marked inhibition of tone of the colon accompanied by a cessation of the rhythmic contractions. The diminution in tone may last for some time after the re-establishment of the rhythmic contractions. I have never observed any traces of a motor effect of these nerves on either coat of the gut. They are not easily fatigued, but may be excited again and again without any diminution in their effects being apparent.

(b) *Pelvic Visceral Nerve*.—This nerve is the motor nerve to the whole colon. Stimulation of either nerve may cause a contraction at any or all parts of the colon. Indeed, the first stimulation generally causes the whole of the large intestine to contract up to a cord. I have endeavoured by the insertion of balloons at different points to determine whether any condition of progression along the walls of the gut is produced as the result of stimulation of this nerve. Apparently, however, all parts of the gut are affected simultaneously, though the action may be more marked in the lower part than in the upper part of the colon. The pelvic visceral nerve is extremely easily fatigued, and it is often impossible to obtain a successful response to stimulation more than half a dozen times in the course of an experiment.

Although in many cases the response to stimulation of this nerve is directly augmentor, in the majority of cases, especially if the intestine be in a state of tone, the first effect is an initial inhibition which is followed by the augmentation. This initial inhibition is exactly analogous to that which is found

in the dog in the small intestine as the result of stimulation of the vagus, and, as in this case, I am inclined to ascribe it to a descending inhibition resulting from contraction of the gut some distance above the balloon, and regard it, therefore, though initial, as only a secondary or mediate effect of the stimulation of the nerve.

The fact that stimulation of the pelvic nerve generally evokes a simultaneous contraction of the whole colon does not, of course, signify that this is the normal mode of activity of the nerve. Stimulation of the vagus causes in the same way a tonic contraction of the whole œsophagus, and yet we know that the normal function of the vagus, as set into action by the first movement of swallowing, is to carry out a peristaltic contraction of the œsophagus. I believe that just as at the beginning of the alimentary canal there is a gradual transition from the cerebro-spinal reflex of swallowing to the local intestinal reflexes of peristalsis, so at the lower end of the gut there is a change in the reverse direction from the automatic reflexes of the upper part of the colon to the spinal reflex which in defæcation affects the lower segment of the large intestine. The control of the central nervous system is therefore limited to the two ends of the alimentary canal. The experiments of Goltz, however, on the effects of extirpation of the lumbo-sacral cord seem to imply that the autochthonic mechanism of the small intestine is not entirely absent even in the hindmost segments of the gut, and that these, when entirely and permanently cut off from spinal control, may after a time develop powers little inferior to those of the small intestine.

I may mention, in conclusion, that on no occasion have I observed any result on any part of the large intestine from stimulation of the vagi or the splanchnic nerves.

In defæcation, the increasing distension of the distal portion of the colon sends up afferent impulses to the lumbo-sacral centres which are gradually summated until a motor discharge along the efferent nerves to the colon is produced. Examination by the Röntgen rays of the process of defæcation in the cat

shows that the first act in defæcation is a rapid shortening of the distal part of the colon, due to contraction of the recto-coccygeus and longitudinal fibres of the gut, followed after some seconds by contraction of the circular coat. This originates at the lower limit of the area of anti-peristalsis, *i.e.*, probably at the upper end of the sigmoid flexure, and spreading rapidly downwards, empties the whole of this segment of the gut. In man the emptying of the rectum is, of course, largely assisted by the contractions of the voluntary muscles of the abdominal walls and pelvic floor.

PART VII.

CONCLUSION.

From the time at which the fertilised ovum begins its development until the death of the individual, an animal's life is made up of a continuous series of adaptations—adjustments of internal to external relations. The changes in the body, induced directly or indirectly by changes in environment, are, in themselves, complexes, the analysis of which it is the office of the physiologist to undertake and to unravel so far as possible the causal nexus between their various constituent phenomena. Although many of the phenomena involved in these adaptations are known to us but as fragments, and though in many cases it is difficult to perceive the chain of causation underlying them, we are firmly imbued with the faith that there are really no gaps over which the interference of some *deus ex machinâ* will have ultimately to be assumed. The physiological advances of the last half century, although tending to discredit the grossly mechanical explanations imagined by some of the earlier workers at this science, have but established on a firmer basis than ever the doctrine of determinism in the living world.

In no department of physiology has the progress in this direction been more marked than in that which is the subject of the preceding pages. Ten or twelve years ago the process of digestion was known only as a series of isolated phenomena, some of which occur in one part, others in another part of the alimentary canal. Now, as a result of the researches of Pawlow and his school, and of those which have been detailed in this essay, we are able to see in digestion an ordered march of events, each step in which is brought about infallibly and fatally by the preceding step, and in its turn acts as the exciting cause for the next step. The initiation of the whole process is bound up with the integrity of the higher centres. It is the sense of appetite and the anticipation of its immediate gratification which determines not only the taking of food, but the primary secretion of saliva as well as of gastric juice. These stimuli are augmented when food is taken into the mouth by the relish with which it is masticated, and the secretion of saliva proceeds until the mass spreads over the back of the tongue. In this situation it is gathered up, and by the stimulation of sensory nerves initiates the chain of motor processes involved in deglutition, which carry with them as an essential part the inhibition of the sphincter which controls the cardiac orifice of the stomach. In the stomach, as we have seen, the food comes in contact with a strong digestive juice, which not only dissolves proteins and connective tissues, but, in virtue of its acid, destroys the greater number of microbes, pathogenic or otherwise, which are swallowed with the food. The presence of the food in the stomach causes a series of movements adapted to the intimate admixture of the food in small quantities with the gastric juice. As the acidity of the stomach contents becomes more pronounced, these movements become stronger, and are associated with occasional relaxation of the pyloric sphincter, so that part of the gastric contents are allowed to escape into the duodenum. The continued secretion of gastric juice long after all idea of food has passed away is kept up by the chemical mechanism we have already described. By the addition of this

chemical mechanism to the reflex secretory process, it is determined that the amount of juice poured out on to any article of food is proportional to the difficulty with which the latter is digested, and is adapted in this way to the needs of the organism.

In virtue of the local reflex mechanism governing the state of contraction of the pyloric sphincter, the stomach is prevented from emptying itself too rapidly into the duodenum. The passage of acid chyme into the duodenum causes a reflex closure of the pylorus which endures until the acid has been neutralised by the outpouring of the digestive juices, pancreatic juice, bile and succus entericus, which make their way into the first part of the duodenum. The secretion of alkaline juices is evoked by the self-same acid food whose presence in the gut requires their addition. As a result of the action of the acid itself, a chemical messenger, or hormone, is formed in the cells of the mucous membrane of the duodenum and carried by the blood stream to the pancreas, the liver and the glands of the intestine. The formation of these juices is, therefore, absolutely proportional to the amount of acid chyme entering the intestine from the stomach. As soon as they have been secreted in sufficient quantity to neutralise the first portions of chyme extruded through the pylorus, the pylorus opens again to allow the passage of a fresh portion of chyme. So the chain of processes is repeated again and again until all the food has passed from the stomach. In this way it is insured that the intestinal digestion occurs in a medium with a reaction which is the most appropriate to the activity of the various ferments involved. A rapid digestion takes place and the end-products are absorbed by the intestinal wall in proportion as they are formed in the gut. The movements of the intestine which determine the thorough mixing of the food with the digestive juices and the onward passage of the food along the gut are themselves aroused by the presence of the food, and their strength is proportional to the distension of the gut, *i.e.*, to the amount of food which has to be moved. As a result, we find that the digestion and

absorption of the food in man is practically complete at the ileo-cæcal valve, all that is left for the large intestine to do being the absorption of a small proportion of water and a minute percentage of food-stuffs which may have escaped absorption in the higher portions of the intestine.

There are, of course, many points which require further elucidation. Thus, the evidence for the formation of a gastric hormone is still incomplete, and we still know nothing as to its chemical nature, or as to that of pancreatic secretin. Yet the whole behaviour of the latter points to its being a body of definite chemical composition and of fairly low molecular weight, and there seems to be no valid reason why chemists should not succeed in isolating and synthesising it as they have done in the case of adrenalin. We have need also of further information as to the cause of the varying behaviour of fats and carbohydrates in their excitation of biliary and pancreatic secretion respectively. The actual excitement of pancreatic secretion when fats are introduced into the duodenum is worthy of further inquiry. In the absorption of food-stuffs there are still many questions to which we can give no answer, or our answers lack precision. We do not yet understand why after excision of the pancreas the absorption of all classes of food-stuffs should be so enormously diminished. The process of de-amination to which we have ascribed considerable importance as occurring in the intestinal wall, rests on but few experiments, and the regeneration of proteins in the mucous membrane after the absorption of the products of protein digestion is still only an assumption, the truth of which is both asserted and denied by physiologists of high authority.

In science, however, no advance is final. Every question solved produces new riddles to answer, since every step higher gives us a wider outlook and the power of seeing problems which, from a lower level, were not apparent. It is this, indeed, that gives to science its absorbing interest and makes it a fit occupation for a lifetime, a lifetime which, like all other phenomena of life, is but a link in the never-ending chain of development of the intellectual powers of the race.

A CASE OF PHLEGMONOUS GASTRITIS FROM HYDROCHLORIC ACID POISON- ING: VOMITING OF THE COMPLETE MUCOUS MEMBRANE OF THE PYLORIC HALF OF THE STOMACH: OPERATION: RECOVERY.

By

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M.A., M.D., F.R.C.P.,

AND

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W. P., æt. 41, in a fit of depression, swallowed about six ounces of spirits of salts* on April 13th, 1910, and immediately afterwards he drank a cup of tea. On Dr. Clarke's arrival a few minutes later, he was given half pint doses of a solution of potassium bicarbonate until the vomit was alkaline. The vomited matter was a dark brown fluid containing mucus and blood. There was no sign of burning on the lips or tongue, but a whitish slough was present over the back of the throat. His pulse being almost imperceptible, the patient was put to bed, packed with hot-water bottles, and given a saline injection. He complained of no pain in the throat, but of a burning sensation and great tenderness in the right side of his abdomen. After

*Spirits of salts are about the same strength as Acidum Hydrochloricum (B.P.).

his bowels had been washed out he was given nutrient enemata every four hours. He continued vomiting a good deal of blood-stained mucus for two days. All this time his throat was very inflamed, and he had difficulty in swallowing even a teaspoonful of water. Each time his throat was swabbed he vomited about a teacupful of stinking pus and debris. This continued for about ten days, after which he was able to swallow freely. A fortnight from the date of the poisoning he was able to take four ounces of milk and Benger's food every two hours. At the end of the third week, as he complained of no pain and there was no tenderness, he was allowed a teacupful of milk and Benger's food every two hours from 6 a.m. till 11 p.m., with a little sponge-cake and bread crumbs. He got up on to the sofa at the end of the third week, and was given jelly, junket and pounded fish with his milk. His appetite was good and he thoroughly enjoyed everything he ate, but he steadily lost weight. He occasionally vomited a little clear fluid, and sometimes his milk. The urine, which at the beginning of the second day became scanty and very high coloured, by this time had become normal, and the fæces, which had been black for about two weeks, became normal in colour. The bowels were opened by enemata every second day.

On May 13th, after a meal containing thin toast, he felt sick and vomited up a cast of his stomach. He was again kept in bed for four days, and given nothing but milk and Benger's food. From the time that the cast was vomited he lost his appetite, and was troubled a good deal with flatulence and abdominal discomfort, but he had no pain. He now took milk in smaller and smaller quantities. He vomited occasionally, and continued to lose flesh and get weaker.

On June 6th he was seen by Dr. Hertz at Guy's Hospital. The stomach formed a visible prominence just below the left costal margin; after some milk had been drunk, it was felt to harden periodically, but no definite peristaltic waves were visible. An X-ray examination confirmed the conclusion made from the abdominal examination—that the pyloric half of the stomach

was practically obliterated, so that food could not enter it. Even on turning the patient on to his right side, no bismuth passed beyond the globular fundus. In a skiagram taken by Dr. A. C. Jordan a narrow shadow could be seen passing from the fundus to the right, which probably represented the remains of the pyloric half of the stomach (Fig. 1).

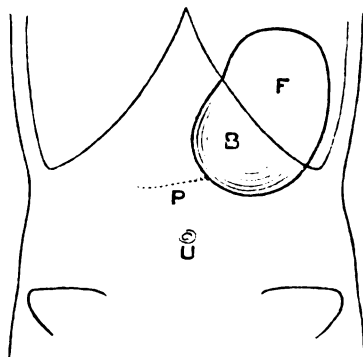


FIG. 1.

Diagram to show the condition of the stomach, as determined by palpation and the X-rays. F = fundus, B = body, and P = pyloric half of the stomach. U = umbilicus.

A stomach tube was passed six hours after the bismuth meal, which consisted of half a pint of bread and milk with two ounces of bismuth oxychloride, no food or drink having been taken in the interval; thirty-six ounces of clear brownish fluid were evacuated with a good deal of bismuth, but only traces of food; some more bismuth was removed on now washing the stomach out.

A test meal of three-quarters of a pint of tea with bread and butter was given on June 10th at 9.30 a.m. The stomach was emptied at 10.45 a.m. and two pints of fluid were evacuated; only traces of bread were visible. Dr. J. H. Ryffel kindly examined the fluid and made the following report: "The gastric contents are acid to litmus, but not to Congo red or Gunzberg's reagent. They contain 0.0036 per cent. combined HCl., and the ether extract gives a good thiophene test for lactic acid,

so that the acidity is mainly due to this acid; butyric acid is also present; the biuret reaction is a definite pink. Proteolytic ferment is present as shown by its rennin action on milk, but the digestion of fibrin is very slow."

A piece of mucous membrane removed from the cardiac sac of the stomach in the course of the subsequent operation was examined by Dr. Gordon Goodhart. It was found to be congested and full of small inflammatory cells. No oxyntic cells were present; this explains the almost complete absence of hydrochloric acid from the gastric secretion. The submucous tissue was also congested and full of inflammatory cells, and there were numerous hæmorrhages into it. In some places the muscular coat was invaded by young connective-tissue cells.

The cast vomited by the patient is six inches long; it forms a bag, which is two and a half inches in circumference at its smaller and eight inches at its larger end. The opening into it at the smaller end is about one and a half inches in circumference; it probably represents the position of the pylorus. A number of smaller fragments were vomited simultaneously. Dr. Gordon Goodhart has kindly made sections of the cast. Most of it is so disorganised that its origin cannot be recognised. Some epithelial cells are, however, present near its inner surface, and on the deeper surface the remains of numerous blood-vessels, some of considerable size, could be distinguished. A few well-preserved fragments of muscular tissue are also recognisable on its outer aspect.

It may be concluded that the cast consists of the whole thickness of the mucous membrane with some of the submucous tissue and muscular coat of the six inches of the stomach nearest the pylorus. Owing to cicatricial contraction the lumen of this part of the stomach has become almost completely obliterated, but it allows fluids to be forced through it with extreme slowness by the very active contractions of the intact fundus. The mucous membrane of the fundus gives rise to an excessive quantity of secretion, but it is much weaker than normal gastric juice, containing only traces of hydrochloric acid and ferments. As the

mucous membrane of the fundus normally secretes a very active and acid juice, it must also have been injured by the spirits of salts.

Mr. Rowlands operated on June 13th. The abdomen was opened through the upper part of the left rectus. The cardiac part of the stomach was so distended that it was difficult to get a view of the pyloric part and of the duodenum, and it was found impossible to bring the posterior wall of the stomach down through the rent made in the transverse mesocolon, although the patient had not had any food by the mouth for nine hours. A stomach tube was passed, and two and a half pints of coffee-coloured liquid and debris, but no gas, escaped. It was now quite easy to examine the stomach thoroughly. The pyloric part was hard and narrower than the first part of the duodenum, which was quite normal. It looked like a narrow and thick-walled piece of small intestine; it was fixed to the posterior wall of the abdomen. The narrowing was most marked five inches from the pylorus immediately to the right of the distended cardiac pouch. From this point a tough thick band extended to the under surface of the right lobe of the liver. The gastro-colic omentum had been drawn up at the same spot, and was adherent to the front wall of the stomach and to the lesser omentum. Otherwise the anterior wall of the stomach was free from adhesions. There were many enlarged and very hard glands in the lesser omentum and about the head of the pancreas. Several recent adhesions were present on the under-surface of the transverse mesocolon towards the right, and the mesocolon was generally shrunken, so that it was rather difficult to make a free opening within the loop of blood-vessels. Owing to the adhesions between the pyloric part of the stomach and the posterior wall of the lesser sac, it was difficult to bring any of the cardiac pouch down through the mesenteric aperture. With the aid of clamps posterior gastro-jejunostomy was performed. The opening in the stomach was three inches long and extended obliquely downwards and to the left to the greater curvature, about three inches to the left of the right border

of the cardiac pouch. The upper end of the opening in the jejunum was three inches below the duodeno-jejunal junction. The mucous membrane of the stomach was inflamed, thin, and very friable. The sero-muscular coats of the stomach were also thinner, and far more friable than natural, so that the sero-muscular suture tore out at several places. The edges of the rent in the mesocolon were sewn to the jejunum just below the anastomosis by means of three interrupted sutures. The patient bore the operation well, and made a rapid recovery.

When last seen, on November 5th, he had gained weight and was able to take ordinary food with a good appetite. He was completely free from pain and had had no abdominal discomfort since the operation. His mental depression had also completely disappeared.

We have been unable to find an account of any similar case, such severe injury to the stomach having previously always resulted in death.

NOTES ON CHLOROFORM NECROSIS OF THE LIVER.*

By

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THE experiments which are the subject of this communication were not originally made for the purpose of investigating the production of necrosis of the liver by chloroform. They were but a means to quite a different end, but they seem of sufficient interest to record, fragmentary though they be, for they approach the subject from a somewhat different standpoint to that of previous observers, and further, although a very considerable amount of work has been done on the subject, it would not seem to have attracted any very general attention.

It is well known that chloroform, if given to an animal in sufficient doses, may, and under certain conditions invariably does, produce a marked change in the liver. This change, originally described as a fatty degeneration, has been defined by later investigation as a necrosis of the cells at the centre of the lobules.

* The expenses of this research were in part defrayed by a grant from the British Medical Association.

Most of these previous experiments appear to have been concerned with somewhat big doses of chloroform. In the very carefully planned series of experiments of Whipple and Sperry* most of the dogs used were anæsthetised for periods of $1\frac{1}{2}$ to $3\frac{1}{2}$ hours, usually twice and often three times, on days in quick succession. Although these observers concluded that necrosis of the liver invariably resulted in dogs after one hour or more of narcosis with chloroform, none of the experiments actually recorded deal with a single anæsthesia of less than $2\frac{3}{4}$ hours duration.

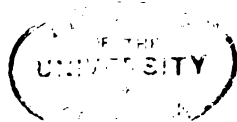
It was my aim to see whether equally constant changes, in less degree, perhaps, could be produced by smaller doses; and, if so, what proportion of cases recover when any marked change has been produced. Whipple and Sperry report that when recovery does take place repair of the liver is complete, even after a most extensive necrosis, in three weeks, and leaves behind no trace of the necrosis.

In my experiments rabbits and rats were used, but the use of rats was discontinued owing to the frequent occurrence of focal necrosis in the livers of rats from apparently independent causes. The experiments here recorded deal only with rabbits. Chloroform was given by inhalation and by subcutaneous and intraperitoneal injection. The inhalation experiments will be dealt with first.

Ten animals were used; they were anæsthetised first with ether† until they were well under, and chloroform was then substituted. Only a very light degree of anæsthesia was maintained, the corneal reflex being present practically throughout the experiments. The administration was continued for periods varying from 30 minutes to 2 hours, and two of the animals were anæsthetised twice on successive days. Great differences were noted in the way the animals took the anæsthetic. Nearly

* John Hopkins Hospital Bulletin, vol. xx., September, 1909.

† A number of experiments have been made by various observers as to the effects of the administration of ether, but no gross histological changes have been produced; moreover, the amount of ether used for inducing narcosis was so small as to be negligible.



all took it badly, and in three cases, in spite of the presence of a brisk corneal reflex, the animal stopped breathing and artificial respiration was necessitated.

The results are tabulated in Table I.

One animal died during anæsthesia after 45 minutes chloroform narcosis; no change could be found in the liver attributable to the chloroform; some fine globules of fat were seen scattered throughout sections stained with Soudan III, but not more than may commonly be seen in an apparently normal animal. In one of the other nine no change could be found; the animal had been anæsthetised for two periods of 20 minutes each on the same afternoon with an interval of an hour between them: it was killed 48 hours later, and the liver appeared normal. In all the remaining eight animals there was a marked change in the liver, varying from a fatty degeneration to a definite necrosis.

The most extensive change was found in rabbit 1, which had been anæsthetised for 75 minutes; but the appearances here and in rabbit 4, which had received two anæsthesias of 60 minutes and 42 minutes on successive days, were almost identical and may be described together. The centre of the lobules is composed of cells of hyaline appearance staining a light pink with eosin; the cell wall is usually intact, but the nucleus stains poorly and is frequently fragmented; here and there are collections of debris, obviously the remains of disintegrated cells. External to these necrotic cells is a ring of empty-looking cells, consisting of a cell wall and a central and often irregular nucleus surrounded by a clear space or a very little granular protoplasm. Around the periphery of the lobule are one or two layers of healthy-looking cells. Droplets of fat are scattered throughout the lobule, but they are much more densely packed in the ring of cells lying immediately internal to the healthy peripheral cells. The capillaries at the centre of the lobule are dilated, but there are few leucocytes. In rabbit V. 3, anæsthetised for 70 minutes, the necrosis is limited to a rim of cells surrounding the central vein, but the cells

external to this rim forming more than the inner half of the lobule are loaded with droplets of fat. In rabbit V. 1, anæsthetised for 40 minutes, there was no necrosis; but the cells of the inner half of the lobule were densely packed with fat, the remaining cells at the periphery being practically free. In rabbit V. 2 the fatty change was much less marked, though strikingly similar in distribution.

In 77 per cent. of those animals which survived the period of narcosis there was, therefore, a marked change affecting principally the cells at the centre of the lobule. A rough glance at the accompanying table (Table I.) might suggest that the

TABLE I.—INHALATION EXPERIMENTS.

Animal.	Length of Narcosis.	Time of Death.	Condition of Liver.
1.	75 minutes ...	Killed in 48 hours	+
4.	{ 60 minutes) 42 minutes)	Died in 54 hours	+
2.	60 minutes ...	Killed in 48 hours	+
V. 3.	70 minutes ...	Killed in 48 hours	+
3.	2 hours ...	Killed in 72 hours	+
5.	{ 12 minutes) 30 minutes)	Killed in 48 hours	+
V. 1.	40 minutes ...	Killed in 48 hours	— Much fatty change.
V. 2.	35 minutes ...	Killed in 48 hours	— Much fatty change.
V. 4.	Died during Anæsthesia	—
V. 5.	{ 20 minutes) 20 minutes)	Killed in 48 hours	—

+ = Central necrosis.

— = No necrosis.

effect on the liver varies directly with the dose. This is, however, not borne out on closer investigation; for example, rabbit 3, which underwent the longest period of anæsthesia, appears half-way down the table, and, moreover, in the case of rabbits 1 and 4, which head the list, the mixture of air and chloroform circulating through the face-piece of the apparatus used contained a much smaller percentage of chloroform than in the case of rabbits 2 or V. 3. This apparent lack of correspondence between dosage and the effect on the liver confirms the impression formed from observation during the anæsthesia, namely, that the toxic effect of the drug runs in no way parallel to the anæsthetic effect, and I quite agree with other observers who report that

the degree of anæsthesia is no measure of the degree of poisoning. Twitching of the limbs, rotatory movements of the jaw, and very rapid breathing may all occur as signs of a deep poisoning in only a very slight stage of anæsthesia.

TABLE II.—INJECTION EXPERIMENTS.

8 Animals injected subcutaneously with 0.5 c.c.

Died within 20 hours	2	+	some fatty change.
Died within 24—48 hours	2	+	more "
Died within 2—3 days	2	+	much "
Killed on 6th day	1	+	
Killed on 16th day	1	—	

+ = Central necrosis.

— = No necrosis.

Eight animals received 0.5 c.c. of chloroform subcutaneously. Of these, six died within three days, and all six showed an extreme condition of necrosis at the centre of the lobules. It may be questionable as to when it is permissible to say from the histological appearances that a particular cell is dead and beyond recovery, *i.e.*, that necrosis has taken place; but in these animals there can, I think, be no doubt whatever. The centre of the lobules (and in many cases as much as three-quarters of the entire lobule or even more) is represented by a mass of red blood cells with the remains of isolated liver cells scattered about amongst them. Some of these liver cells are intact with nucleus and surrounding protoplasm, the latter hyaline, staining light pink with eosin, the former mostly fragmented: others consist merely of free nuclei with perhaps a little granular protoplasm left attached to one side, or again, a mere granular mass of debris. The amount of fat present varies considerably. In the cases where the necrosis is most extensive it is present in greatest quantity in the cells still left intact at the periphery of the lobule; in the less advanced cases it is massed in large droplets in the cells lying between the necrotic area and the

peripheral cells. There is a certain amount of fat scattered about in globules in the necrotic area, but to a very much less degree. Further, the fat is most abundant in those animals which have withstood the poison longest. In the animals dying within twenty-four hours it is relatively small in amount, in those which died on the second day it is present in definitely larger quantity, and it reaches its largest amount in an animal which lived till the third day. Previous investigators seem to have concluded that the process involved was a primary fatty degeneration passing on to a complete necrosis; but these observations afford some support to the view I have formed from a consideration of the whole series, that where the toxic action is sufficiently intense the necrosis is the primary change, and that a fatty change is only observed in lesser degrees of poisoning.

The degree of toxicity may, of course, depend either on the concentration of the poison or the susceptibility of the cells; a stronger concentration at the centre of the lobule would be contrary to expectation, and difficult to explain, and it is therefore possible that the central cells are more susceptible and therefore die; the cells outside these, being less susceptible, undergo a fatty change, and the peripheral and least susceptible survive as normal.

Of the two remaining animals one was killed on the sixth day and one on the sixteenth day. The liver of the former showed definite necrosis around the central vein, but it was small in extent, the outer seven-eighths of the lobules being composed of quite healthy-looking cells. At the centre of the lobule the regular arrangement of healthy cells is replaced by an irregular open or reticular framework containing liver cells in all stages of degeneration, mixed with large numbers of red blood cells and small round cells; in addition to these there are large numbers of liver giant cells. These consist of large masses of protoplasm, staining with eosin like liver cells, surrounding a conglomerate mass of nuclei; the largest are found near the junction of the healthy and necrotic area.

those in the actual centre being mostly smaller degenerate forms without a definite cell wall. The nuclei vary in number from a single fused mass of nuclear material to ten or more more or less distinct nuclei. There is a large quantity of yellow pigment in all these giant cells, though it is conspicuously absent from all the other cells whether in the central or peripheral area. In the central area there is also much fat, chiefly in the form of fine granules massed together; these are found alike in the ordinary necrotic cells and in the giant cells.

The liver of the animal killed on the sixteenth day is apparently normal. There is no increased amount of fat and no evidence of a previous necrosis.

Thus, of the animals which received 0.5 c.c. of chloroform subcutaneously, 87.5 per cent. showed definite central necrosis of the liver.

Injection of 0.2 c.c. of Chloroform.—The chloroform was injected either subcutaneously or intraperitoneally. I have not been able to trace any difference in the results obtained from the two methods, and for convenience sake they are here grouped together (Table III.).

TABLE III.—SUBCUTANEOUS INJECTION OF 0.2 C.C.

No. of injections.	No. of Rabbits.	Died with- in 12 hours.	Died or killed within 10 days.	Died or killed within 10-20 days.	
1.	34	0	2 d. + + 5 k. — — — — —	2 k. 10 d.	All —
2.	15	1 —	1 d. —	2 d.	
3.	11	0	4 d. — — — —	2 d.	
4.	5	1 —	0	0	
5.	2	0	0	0	
6.	2	0	1 d. 1 k.	

+ = Central necrosis. — = No necrosis. k. = Killed. d. = Dead.

The results of the series are much more complicated, and I shall merely state them briefly. I cannot attempt to explain them at present.

None of the animals of this series showed any anæsthetic effects from the dose. Within a few minutes of the injection they were frequently found to be lying stretched out with the head strongly retracted and breathing shallowly with great rapidity, and this condition lasted not infrequently for several hours: but they responded to stimuli always, and if their position was altered they would frequently take a few jumps round the cage before resuming their original position.

Thirty-four animals received 0.2 c.c. subcutaneously or intraperitoneally; of these two died on the fifth day and both showed a central necrosis of the liver equal in extent to anything found in the previous series; the histological changes in these two were exactly similar to those already described, and need not be repeated. Five were killed within the first five days, and none of them showed any central necrosis, but extensive central fatty degeneration was found in three, less marked change in one, and one was apparently normal. Two were killed and ten died within twenty-six days. In none of these was there any central necrosis or fatty degeneration at all similar to that previously described. I will speak of the condition found here later.

The remaining fifteen animals were re-injected with the same dose twenty-six days later; of these one died within twelve hours, one within ten days, and two within twenty-six days. None of these showed any central necrosis or fatty degeneration. The remaining eleven animals were again re-injected, the survivors receiving a fourth injection, and so on; only one animal survived a sixth injection, and this was killed. The results are shown in the table. In none of these re-injected animals was any change found in the liver at all comparable to that found in those dying or killed after the first injection. These animals do, however, show a definitely increased mortality; other animals not injected and kept under the same conditions and in the same house lived on happily, while the chloroformed rabbits died off.

The livers in these animals, although in no way resembling those of the animals of the previous series, do all present a more or less similar picture, and one that must, I think, be abnormal. Firstly, they tend to be very full of blood; the central veins are often greatly distended and packed with red blood cells; radiating from these are greatly dilated capillaries also full of red cells and compressing the adjacent columns of liver cells, so that in many cases the field presents a picture of broad columns of blood cells with a mere chain of nuclei of liver cells surrounded by an attenuated cord of protoplasm connecting them. Secondly, the central vein is often lined by a thick pinkly staining wall of connective tissue, of a thickness of three liver cells, whilst in other cases the outline of the central vein has entirely disappeared, the vein being represented by an irregular space, without a definite wall, filled with a grey granular material which often contains small colonies of liver cells imbedded in it. Here, too, the red blood corpuscles form a very striking picture as they lie amongst the liver cells, and often there are definite areas of hæmorrhage in close proximity to the central vein.

Various observers, especially in France, speak of a second form of change in the liver produced by chloroform which they term "hæmorrhagic," and which may perhaps resemble the condition here described. For a satisfactory explanation of this condition I am entirely at a loss, but it is possible that there has been some destruction of the cells at the centre of the lobule originally, and that in the process of regeneration of the liver cells the re-formation of the central vein has been incomplete, or in some way interfered with.

The method of repair and the extent to which it occurs is too lengthy a subject to be treated of here, and must be left for a future occasion.

In conclusion, a few words may be said concerning the effect of chloroform on the liver in man. The association of an extreme necrosis of the liver with cases of delayed chloroform poisoning is now well recognised, and a condition of the liver closely resembling that in acute yellow atrophy has been found

in practically every case in recent years in which an histological examination has been possible. But in view of the ease with which an extensive necrosis can be produced in animals, even with comparatively small doses, it is reasonable to wonder whether in the human subject also, where chloroform is used as an anæsthetic, similar changes of milder degree may not occur in patients whose susceptibility to the drug is not sufficiently great to involve them in a general poisoning.

Two cases which I have had the opportunity of examining in the post-mortem room this year give some support to this suggestion.

Case 1.—A. S., a child of 6 years, was operated upon for a cleft palate; chloroform was used throughout, but I have been unable to obtain any exact details as to the length of the anæsthesia. The child died twenty-four hours later, but there appear to have been no symptoms clinically pointing to chloroform poisoning. At the autopsy, no macroscopic changes of importance were found in any of the organs, but the liver showed extensive alteration on microscopical examination. At the outer edge of the lobules are a few rows of clear empty-looking cells with healthy nucleus and intact cell wall, many of them containing vacuoles from which the fat has been removed. The central three-quarters of the lobule are occupied by an irregularly arranged mass of much more deeply staining cells, many of which, apart from an increase in the amount of stainable fat, have the appearance of healthy cells, but mixed up with these are large numbers of necrotic cells. In some of these the protoplasm takes on the dull pink stain in eosin preparations characteristic of early necrosis, the nucleus remaining intact and deeply staining; in others, the nucleus is fragmented or has entirely disappeared; many other cells are merely represented by a shadowy mass of granular debris. The capillaries in this area are widely dilated, and the red blood cells lying mixed up with the necrotic liver cells form a prominent feature of the section. There is, therefore, in this case a central necrosis which very closely resembles the condition produced experimentally in animals.

Case 2.—K. B., a small girl of 7 years, was operated upon for osteomyelitis of the tibia, A.C.E. mixture being used throughout; a fortnight later a second operation was performed to explore the hip joint, A.C.E. mixture being again used. The child did not take the anæsthetic well, and towards the end oxygen and a hypodermic injection of strychnine were given, and ether was substituted for the mixture. The child died twenty-four hours later. Post-mortem, apart from the local condition of the leg, no gross lesion was found in the organs except an early hæmorrhagic pericarditis. The liver was rather pale, but otherwise showed no naked-eye change. Microscopical examination showed extensive central necrosis. The inner half of all the lobules is composed of completely necrotic cells with only an occasional healthy cell scattered here and there amongst them. Mingled with these necrotic cells are a very large number of polymorphonuclear leucocytes and fewer large mononuclear cells; the leucocytes are in some cases limited to a broad zone at the junction of the healthy and necrotic areas, but in others they are equally distributed throughout the entire necrotic area. The outer half of the lobules is composed of apparently healthy cells, and there is very little, if any, increase in the number of leucocytes in this area. The portal canals are entirely free from any inflammatory reaction.

There were, of course, in this case other factors than the chloroform which might be held responsible for the damage, for the child was suffering from a severe septicæmia; but where necrosis of the liver occurs in septicæmic conditions, the necrosis is usually of the focal type, such as is commonly seen in cases of eclampsia. I have now examined the liver in 20 cases of death following operation, and the only other case of definite necrosis was of this focal type; here the patient had undergone a prolonged intestinal operation under ether administered by the open method.

When the picture of central necrosis characteristic of the experimental lesion is so faithfully reproduced as in the two

cases described above, it is difficult not to look upon the chloroform as the causative agent.

Amongst the other cases pure chloroform was only used in two; in one of these, a case where chloroform was given for the opening of a mastoid abscess, no necrosis was found, but there was a marked increase of fat around the central vein, a condition very closely resembling that in rabbits V. 1 and 2 in Table I. In the other the child died from pneumonia a fortnight after the opening of an empyema; and judging from the experimental lesions, one would not expect to find any evidence of a previous necrosis remaining at that length of time.

Two other patients died after operations for strangulated hernia at which A.C.E. mixture was used throughout; one died eight hours after the operation, an interval apparently too short for the appearance of the characteristic lesion; and in the other, who survived for twenty-four hours, no change in the liver was found.

In the remaining cases, where ether alone was used, I have found as yet no case of central necrosis or fatty degeneration.

VARIATION AND MENDEL.

SOME OBSERVATIONS ON THE CROSSING OF WILD RABBITS WITH CERTAIN TAME BREEDS.

By

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It has been long recognised (i.) that all living matter is undergoing change; (ii.) that in all living matter which persists these changes are cyclical.

That this is true of each individual species may be realised by consideration of the life-history of all animals or plants whose life-history we know sufficiently well. If these premises are well founded, then, I think, it follows that each completed cycle, or what we call the individual, of the moment should be a replica of the individual of yesterday, and yesterday's of the day before, and so back to the beginning. This we may regard as the normal course, the course which, so to speak, ought to be followed, but owing to the occurrence of deviations from the normal course, which we speak of as "variations," any one life-cycle is probably never an exact repetition of that immediately preceding it.

If it were true that each individual is an exact replica of the individual, or each completed cycle an exact repetition of the completed cycle which preceded it, then, clearly, every cycle or generation would be simply an exact reproduction of the first cycle of all. This could only be so if no evolution had taken place.

But we know that deviations from the normal are frequently occurring which introduce new phases into the life-history, so that to-day's life-cycle will be yesterday's cycle altered by variations (either in the form of additions or subtractions) due to the deviations just referred to. And this has been going on, perhaps, at each repetition of the cycle since the species started on its course thousands or millions of years ago, so that to-day's life-cycle is not only to-day's with an addition caused by variation occurring to-day, but is the net result of the sum total of additions which have been made and of the total deficiency due to all that has been subtracted from time to time at the countless previous cycles.

Thus the development of the present individual represents the evolution of the race in a more or less complete manner according to whether the subtractions have been small or great. As a general truth this must be so; at least it seems to me that it is the only logical deduction from the premises that living matter is constantly undergoing change, and that those changes are cyclical in all living matter that persists. But it should be clearly understood that the ontogenetic record implied by the above reasoning is a record through development and of development; it is not a stringing together of "adult" forms. So that if we wish to state the conclusion as a "law," we must say not more than this: "The development of the individual tends to indicate the course taken by the species in its evolution." Stated thus, the recapitulation theory may be said to be one of the fundamental principles of biology, but in reality the fundamental principle involved is the cyclic character of the growth of organisms, which is also the fundamental principle of heredity—and it is to be regarded as the normal course, the course the life line would take if it were not for disturbing causes. By the phrase "normal course" I mean the course that would be taken due to past causes if not interfered with by present or future changes of conditions, just as the normal course for a body to pursue if once given motion in a definite direction is to continue to move for ever in a straight line in the direction imposed upon it by the original impulse.

We thus arrive at the conclusion that in the normal course of events each successive completed life-cycle should be an exact repetition of the life-cycle immediately preceding it. This we express in ordinary language by the aphorism "Like begets like." It is the fact of heredity. This, a very marvellous phenomenon no doubt, is really less remarkable—seeing that the tendency for protoplasm is towards rhythm—than that the offspring should be unlike the parent. Having recognised the fact that repetition or heredity is the normal, we ought to inquire next whether we can gain any idea as to how this is brought about. What, indeed, is the process by which a repetition of a life-cycle is approximated. This would involve the whole question of growth, that is to say, the question of individual development, so that one is led to the conclusion that heredity and the normal development of the individual are synonymous terms. The question as to how this growth along specific lines occurs, that is to say, what ordains the orderly formation of tissues and organs at the proper moment, is the problem before the embryologist, and is outside the aim of the present article. But nevertheless it is the essential problem of heredity. Darwin's famous theory of pangenesis really leaves the actual question of development, and therefore of heredity, unattacked. It attempted to account for the collection within the germ cell of all the characters to be repeated. But it made no suggestion as to how this repetition is to be brought about. The same objection may be offered to most of the other theories of heredity which have been propounded since, and which bear close resemblance to Darwin's original suggestion. It is no explanation of the fact that a bird's egg develops into a bird like the bird that laid it, to say in effect that it does so because it contains thousands of smaller "eggs" or particles within it, each of which at the right moment "develops" into, or determines the development of a certain part of the bird—whether such particles are called gemmules, pangens, ids, engrams or factors. What we have to aim at first is to answer such questions as why a cell divides, why the egg segments, why a blastula

forms, why a gastrula results, and how a gastrula is formed, and so forth. So we are led to the conclusion that as a result of the rhythm or cyclical tendency of all protoplasm that persists, therefore of every separate life line, each cycle should be a complete and perfect repetition of the one preceding, and therefore that development, heredity, and recapitulation are synonymous terms. It is one problem.

But just as we saw that on account of the occurrence of deviations from the normal, either by addition of some new integer, or by the subtraction of an old one, the recapitulation is never exact, and could only be exact if there had never been any evolution, so in the life-cycle compared with the immediately preceding life-cycle, the "heredity" is probably never an exact inheritance.

Under the general term Variation we must include all the types of deviation which may occur from the normal which make the inheritance never an exact inheritance. So far as I can understand the matter there appear to be three distinct types of deviation or variation. Anyhow, whether they are distinct or not, we can for convenience classify them as under:—

1. Fluctuational,
2. Mutational,
3. Amphimixial,

so that whenever a life-history deviates from the normal, that is to say, whenever inheritance is not exact, it is due to a variation of one or more of these types:

1. By a *fluctuational variation* is meant one which is due to some disturbing influence, external or internal, which, while it acts, produces a deviation from the normal, but if the disturbing cause is removed it leaves no permanent effect. So that if in the succeeding life-cycle the disturbance is not there, then the deviation will not occur. A fluctuation leaves no permanent impress upon the species. To make this clear I might use as a simile the following illustration: I have a large wheel which revolves slowly, and whose rim is elastic and flexible. Each revolution may represent one complete life-cycle—one "gene-

ration," in fact. We will number the spokes 1, 2, 3, and so on, in order to be able to identify any one period of the life-history. Now, I watch the revolution of the wheel: whenever spoke number 10 comes round I press my hand against the rim till spoke number 12 has passed. Each revolution I perform this operation, and at each revolution the rim is deflected. A fluctuation has been initiated. I cease to apply my hand and the revolutions of the wheel are like they were before I applied my hand; there is now no fluctuation, no deviation from the normal. The wheel itself has not been permanently affected. Of such a nature are the modifications brought about during development by external environment, special feeding, maiming by such mutilations as circumcision, compression of feet, or the heads of infants, and so on.

2. A *mutational* variation is a deviation from the normal which affects the individual to so great an extent as to cause a permanent alteration in the life-history, and so to create a new character either by addition or subtraction. To turn to my former simile. The wheel is revolving, but this time I touch the rim, not with my hand only, but with a brush filled with paint. A permanent character is now apparent on that part of the rim every time it comes into view. Something has been added; or, I knock out a spoke, something has been subtracted. A mutation has arisen. Such are "sports" which appear among plants, and such by hypothesis are vast numbers of characters which are due to causes other than that described next, namely:

3. The third or *amphimixial* type of variation—if I may venture to use such a term. This is due to the fact that in the vast majority of life-cycles the organism is, during a part of its life-history, of the nature of a double individual, owing to the co-partnership entered into at the gamete stage of the life-cycle. Each gamete that enters the co-partnership has, as a rule, had a separate ancestry, and so during the development of the combination individual, which is the condition of all the ordinary animals and plants, it is conceivable that the combination individual may follow either the one or the other normal, or may

take an intermediate course and so be unlike both, but it cannot follow both normals exactly unless the normals are exactly alike.

Thus we have in sexually produced animals or plants variations from the normal which are neither fluctuations, nor mutations, but which are due to amphimixis.

(The word "amphimixis" was coined by Weismann to express the idea of fusion of the germ plasms and their hereditary qualities as a result of the union of gametes.)

It is with characters due to this type of variation that the Mendelian principle is concerned. If we accept the idea of heredity as the normal, and variation the deviation from the normal, then the law of Mendel is a law of heredity only so far as it affects the distribution of parental characters in sexually produced offspring. It is a law of variation, strictly speaking, rather than a law of heredity.

The Mendelian principles are evidenced in two quite distinct ways by the fact of co-partnership of life-lines brought about by the fusion of gametes.

i. There is the effect which the two partner gametes have immediately upon one another, which is, so to speak, evanescent, perhaps fluctuational. This concerns the F 1 and certain members of the subsequent generations, *e.g.*, the phenomenon of Mendelian dominance in all its grades.

ii. The effect, which is a permanent one, upon the life-lines themselves, so that when the partnership ends, that is, at the next gameto-genesis, the life-lines *may* have become altered, characters which belonged to one life-line may have passed into the other, and *vice versa*. This is the phenomenon of Mendelian segregation. (An analogous phenomenon is perhaps to be recognised in the way in which one life-line of a protozoon, say of *Paramecium*, will for a while enter into co-partnership with another and then separate, but during the temporary union an interchange of protoplasm has been effected, so that when the individuals representing life-lines separate they are different to what they were before.) The effect of this is not seen till the F 2 generation.

Having thus attempted to define clearly the differences between heredity and variation, we may turn to the consideration of the distribution and rearrangement of characters according to Mendel's law, a subject which has great importance for breeders of all kinds, for horticulturists and farmers alike, for human society in general, and for medical men and students of organic evolution in particular.

Mendel's experiments were made chiefly upon varieties of the ordinary garden pea, but, as is well known, subsequent workers have tested and confirmed and extended his conclusions from many types of animals and plants. For detailed accounts of these experiments the reader must turn to the works mentioned at the end of this article, more especially to Professor Bateson's book, "Mendel's Principles of Heredity," where the details of many experiments are given, together with a masterly account of the whole subject, and to Professor J. A. Thomson's "Heredity," which contains a résumé of many authors' views, and other theories of heredity.

The essence of Mendel's law of variability, if I may so name it—for from the point of view assumed in this paper it concerns *variability* rather than heredity—is that the differing characters which are brought into co-partnership by the two gametes of different ancestry do not necessarily combine into permanent alliances, but remain apart, and on the cessation of the union, which practically occurs on or before the formation of the next generation of gametes, these characters segregate, so that some pass into one gamete, others into another. In the ordinary way individuals which interbreed show but small differences in their characters, or else the differences are complex, but in the case of many "cultivated" plants and domesticated animals there are many sharply-marked characters which may be traced easily through succeeding generations, and so the latter type is more convenient for experiment. (There are exceptions to this statement, as, for instance, the pin-and-thrum character of primula.) For descriptions of generations of individuals studied from the point of view of heredity and variation, it

has become customary to denote each generation by the following symbols: The original pair of a line studied is known by the letter P, or parental generation. The offspring of P ♂ mated with P ♀ gives a generation known as F 1, or first filial generation. The next generation produced by the interbreeding of the F 1 individuals results in the F 2 generation, and so on.

As the result of Mendel's experiments, and many others performed recently on Mendel's system, it has now been proved in many instances that if two individuals are mated, the one having a character which is absent in the other, or which is represented in the other by a distinctly different character, then the hybrid offspring (the F 1 generation) of this pair will be all like one another, and either like one or other of the two parents, or like neither. Obviously they can never be like both unless the parents are identical. If these F 1 generation individuals are bred together three types are produced (F 2 generation), namely, one type presenting the character of one grandparent, another type with that of the other grandparent, and the third type like the parents with respect to this particular pair of characters. Moreover, if large numbers are dealt with in the experiment, it is found that these three types of the F 2 generation occur pretty accurately in definite proportions, namely, one like each grandparent and two like the hybrid parents.

If individuals which resemble one of the two grandparents are bred together their offspring are all like themselves and the one grandparent, and their offspring will again breed true, and so on. If, however, the individuals which are intermediate are bred together, the result is the production of three types, as when the F 1 hybrids were bred together, namely, some like one grandparent, and some intermediate, and some like the other, and if large numbers are dealt with, they occur in the proportion of

$$1 : 2 : 1$$

Mendel's explanation of this fundamental fact which he discovered was that a hybrid gives rise not to hybrid sex cells (gametes), but to sex cells which contain either one or the other

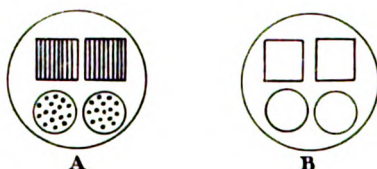
character, never both. In other words, although the hybrid individual itself is the product of two influences—it is a hybrid—yet the germ cells which it gives rise to contain the influencing factor of only one of the pair of characters considered. The characters which are mingled in the hybrid segregate during the formation of the germ cells, and pass one into one, one into another germ cell. He further supposed that the hybrid gives rise to the average to equal numbers of germ cells bearing one or the other factor or determiner, as it is called. Thus, when hybrids which have been created by the mating of two forms (which we will call D and R), are mated, there are equal chances of a spermatozoon bearing the factor, let us say D, meeting an ovum bearing the factor D or a spermatozoon bearing the factor D meeting with an ovum bearing the factor R, or of a spermatozoon bearing the factor R meeting with an ovum bearing D, or a spermatozoon bearing R meeting an ovum bearing R, the result being four types of individuals whose composition may be expressed as DD, DR, RD and RR. Since DR is the same as RD we have the result 1 DD : 2 DR : 1 RR.

But it probably never happens that animals or plants differ from one another in respect of a single character only. Usually the differences concern many points, in which case since each pair of differences may behave independently of the other pair, the result of crossing is much more complicated.

The accompanying diagram is intended to illustrate graphically the effect of mating in respect of two pairs of characters which are here represented by the hatched and blank squares and the dotted and blank circles respectively. The two types of squares form one pair of characters (Professor Bateson's allelomorphic pair), the two types of circle a second allelomorphic pair. One individual is supposed to have the characters represented by the hatched square and the dotted circle, the other by the blank square and blank circle.

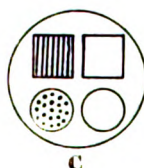
When these individuals are mated their offspring will be hybrids, formed by the fusion of gametes of the two individuals. It is presumed that the parents were pure bred, that is to say,

the one parent was formed by the fusion of spermatozoon bearing the hatched square factor and dotted circle factor with an ovum bearing also the hatched square factor and dotted circle factor, so that its composition may be represented by this dia-



gram A, while the other parent was formed by the fusion of gametes bearing the blank factors. This will be represented by the diagram B.

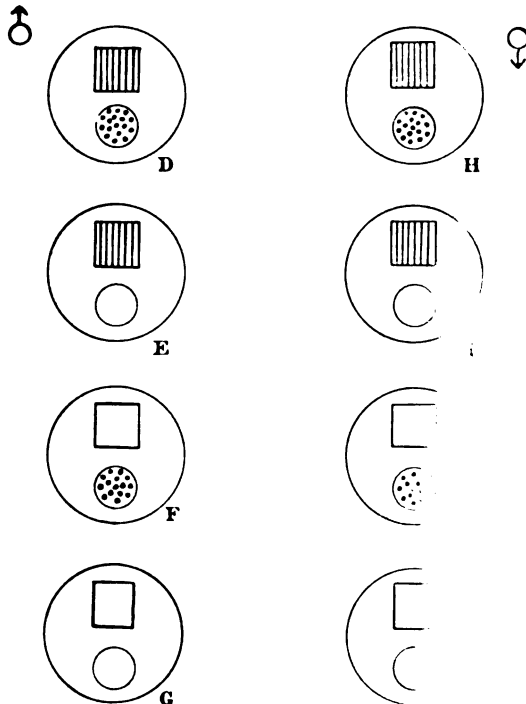
At the first cross, the F 1 generation, each individual will be a hybrid whose composition is represented by the diagram C.



When the hybrid forms its gametes these factors segregate and pass into separate gametes, so that the gametes of the male (the spermatozoa) will be represented by either D, E, F or G. No gamete will have more than one of each pair, and presumably each will have a representative of each pair. Thus, there are four different combinations possible, as shown by the diagrams D, E, F, G, and the gametes (ova) of the female will be represented similarly by the four possible types of combination H, I, J, K.

On Mendel's hypothesis each male hybrid will be producing all four types of gametes on an average in equal proportions. So also will the female.

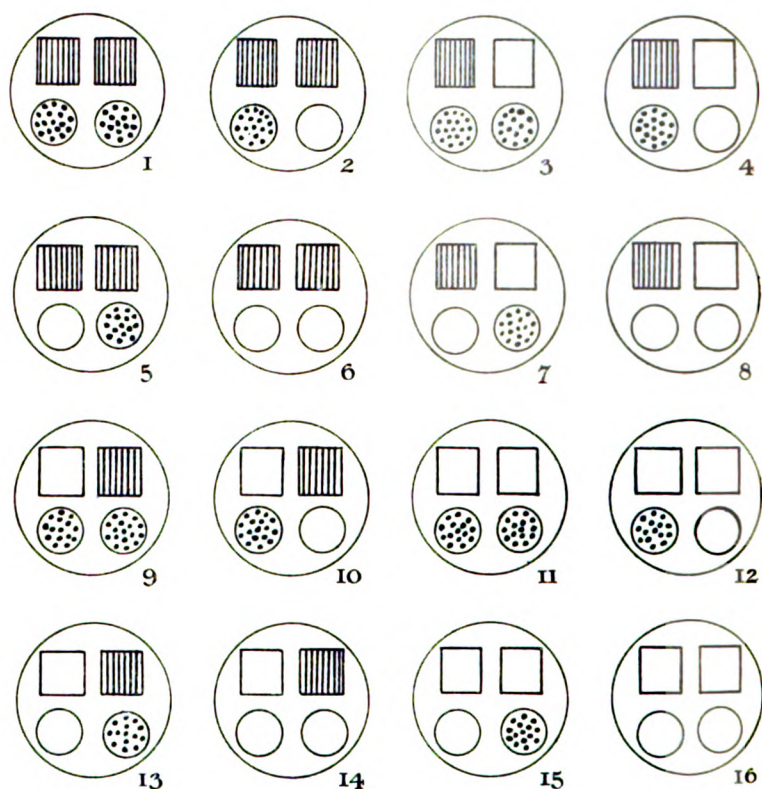
Thus, when the hybrids are mated there will be equal chances that a spermatozoon with the composition D will meet and



form a partnership with an ovum of the composition H, or with I, or J, or K, thus producing four different types of individual which we will arrange on the top, thus: 1, 2, 3, 4.

So one may take a male gamete of the composition E and put its four possible combinations in the second line 5, 6, 7, 8, and so on till one gets the sixteen possible final combinations.

Now a glance at the diagram shows that all those individuals along what I may call the N.W. and S.E. diagonal, namely, 1, 6, 11, 16, are different from the others in having only two kinds of characters. Take any one of these types and breed the individuals of this type *inter se*, and it will be found that they give rise to nothing else but their own sort. Each individual contains only two kinds of factors, and, obviously, distribute them as you will amongst the gametes, on fusion again at the time of fertilisation only the same combination can be made. Therefore, all these are pure types or homozygous, as they are



termed, and each type, when mated with its like, will breed true to those characters.

On the other hand, all the individuals along the N.E. and S.W. diagonal (along the "bar sinister"—they are as bastard as they can be) are alike in that they are constituted like the hybrid F1 generation, and each type should produce the same series as shown in the diagram, if individuals of each type are bred *inter se*, or if individuals of any of these four types are interbred. These are all heterozygous, and bear all the characters. Similar calculations may be made with reference to the remaining ones, with definite results which need not concern us at the present. It must be noticed

that among the sixteen possible combinations of the factors of the two allelomorphic pairs there are only nine actually different types, so that there would be the possibility of nine different types among the offspring of the F 2 generation, forming a series of types, which, if large numbers are dealt with, will form a series in the proportion of 1, 2, 1, 2, 4, 2, 1, 2, 1. the "ones" alone being homozygous, and therefore capable of breeding true.

I have gone far enough now to illustrate what I meant when naming the third great type of variation amphimixial. Amphimixial variation or deviation from the normal is inevitable in all organisms in which the fusion of gametes forms a necessary condition for the continuance of the life-line, unless, of course, the gametes are of the same ancestry or are the bearers of absolutely identical qualities. This exception theoretically occurs whenever two similar homozygous individuals mate.

In such cases, so long as the breeding is always between identical homozygous individuals, no permanent amphimixial variation can occur. The only variation will be the fluctuational, and now and then a mutational variation, which latter event, *per se*, destroys the homozygousness of that species, and at once gives opportunity for the further amphimixial type of variation. In any one species probably all individuals are homozygous for the nine hundred and ninety-nine out of every thousand factors which lead to the construction of a certain type; the one heterozygous factor being perhaps that of a superficial, but very conspicuous character, as, for instance, colour of fur or character of feather. From the great rarity, so far as it is known, of the heterozygous state in nature one may reasonably suppose that the effect of natural selection is towards discouragement of the perpetuation of heterozygous forms.

So long as conditions are stable, a homozygous form, if a suitable form, would have an advantage in the struggle for existence over a heterozygous form from the fact that, *ceteris paribus*, it would have a numerical advantage in point of offspring. How great is this possibility may be deduced from

calculating the effect of a heterozygote which paired with a heterozygote producing eight offspring in the ratio $D : 2 DR : R$. If each of these pairs with a type similar to itself, and each again produces eight young according to expectation, then at the end of the fifth generation, each always pairing with its like, there would be of the fifth generation 992 $D : 64 DR : 992 R$. Compare this with the result of a homozygous individual, which by the same means might have produced 2048, and some idea will be obtained of the initial numerical advantages a homozygous type *may* receive over a heterozygous form.*

In the table just given I would draw attention especially to two individuals, No. 6 and No. 11. These are two of the four homozygous types. The other two, 1 and 16, are like our original pairs, the P generation, and each type should breed true to the original type. But No. 6 and No. 11 are two quite new pure types which are as fixed as any natural variety can be fixed. That is to say, by the simple process of crossing, or amphimixis, two new varieties as pure as the original ones have been brought into existence. For the proofs that plants and animals do behave with respect to certain characters as they should according to this table, I must refer the reader to the works of Mendel himself, and of those who have during the last eight years demonstrated the truth of his hypothesis of segregation of character factors during gametogenesis.

There is in chapter iii. of Professor Bateson's book, "Mendel's Principles of Heredity," on pp. 61—8, an account of experiments in connection with the inheritance of the combs of fowls which is one of the most fascinating and illuminating sections in the book, and which deals with the ingenious "presence and absence" theory, which seems to me to support very clearly, or at any rate illustrate very well, the meaning I had in view when I spoke of "Heredity" being synonymous with Development, and maintained that it should be regarded as the *normal* course the life-line would pursue if it were not for the deviations caused by

* If the pairing is such as to favour the heterozygote formation, the most favourable result possible would be 352 $D : 1344 DR : 352 R$. In the long run the advantage is with homozygousness.

the several types of variations under consideration. Thus he shows how the rose comb and the pea comb are recent variations—how they started we cannot say—though we may suppose that they were added to the life-cycle as mutational variations in the place of the original single comb of *Gallus bankiva* which “we are fairly safe in regarding as the primitive or original form from which all the others have been derived.” Bateson shows that he has been able by means of suitable crossing to remove the factor for the pea comb and the factor for rose comb, and has obtained the single comb which is the old original comb of the wild species, and, secondly, by combination of the two factors has obtained a fourth type, that known among breeders as “walnut.”

Thus we seem to have in this experiment an example of a mutational variation in the rose or pea comb which has supplanted the “normal” single comb in certain breeds of poultry. In the walnut comb we have an instance of a strictly amphimixial permanent variation produced by the combination of the two factors for rose and pea, effected on the principle known as Mendelian segregation. But not only does the Mendelian principle of segregation, by a shuffling of the characters during co-partnership of the life-line, lead to new combinations by addition, but it may sometimes disclose in reversion an ancestral or older type, through the removal of what we must suppose was a mutational variation, as in the case of the appearance of the single comb as here demonstrated by Bateson. But an ancestral type may be obtained in another way, namely, by recombination of factors which had been at some previous period separated owing to Mendelian segregation, as in the case of the Sicilian pea described on page 88 of Bateson's book.

Now I have in my table above shown that in dealing with the combination of two pairs of allelomorphic characters we obtain nine types of offspring in the F₂ generation.

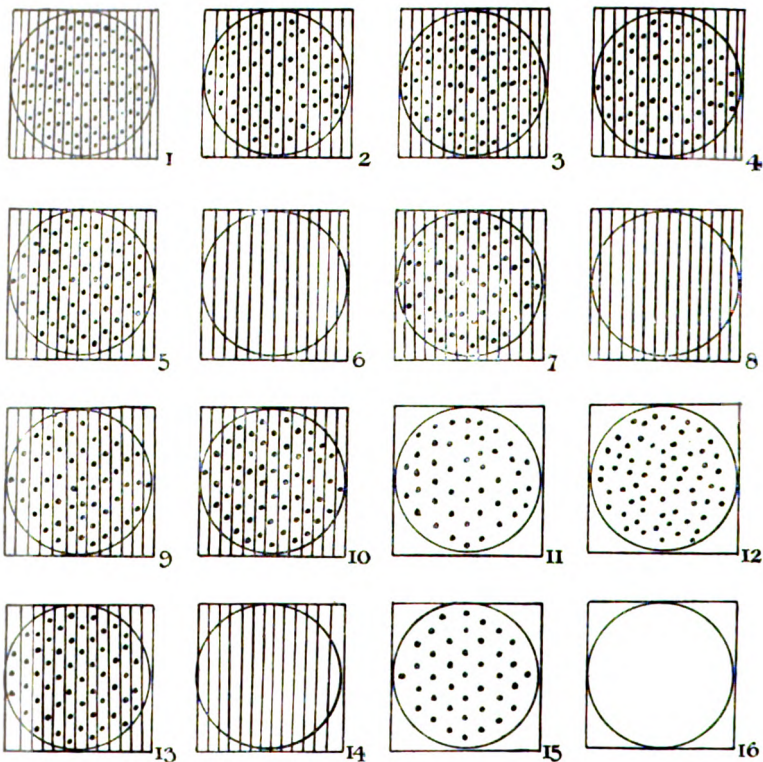
Owing, however, to the fact that often in the hybrid one member of a pair of allelomorphic characters is more in evidence than the other, this member may mask the other so much that one would not suspect the presence of the latter. This pheno-

menon Mendel called Dominance, and the evident character Dominant, and the other factor which is often unnoticed in the hybrid he called Recessive.

Thus, to take the simplest case, if an individual D, with a character which is the dominant one of a pair, is mated with an individual R having the other character, the F 1 generation, DR, although hybrids, may look all like D, or at any rate so closely like D as to be distinguishable only with difficulty.

Then, at the F 2 generation, when DR is mated with DR, the offspring are, of course, as usual, really in the proportion 1 DD:2 DR:1 RR, but owing to the phenomenon of Dominance, the DR individuals are not to be distinguished externally from the DD individuals, so that the proportions appear to be

$$3 D : 1 R$$



It is only, in this case, by breeding from each individual that it is possible to determine which are the pure ones and which the hybrid. The phenomenon of dominance in some ways simplifies, in some ways complicates, the determination of the nature of the individuals. As we have seen, it renders it more difficult to differentiate individuals in the F₂ generation in a simple case like that just given. To a certain degree, and in rather a useless manner, it may be said to simplify the result, as in such a diagram as that given on page 16. If in this case the hatched square were perfectly dominant over the blank square and the dotted circle over the plain circle, we should be unable to differentiate visually between many of those containing the dominant characters, and an F₂ generation might show four or three types only instead of nine, which would form the series 9 : 3 : 3 : 1, or 9 : 3 : 4.

SOME BREEDING EXPERIMENTS.

The observations recorded below were originally begun with the idea of endeavouring to follow the chromosomes of the different varieties of rabbits, but the task has proved too difficult. The rabbits have also been used for embryological purposes, so that the experimental work was not the only object I had in view in keeping the animals. I kept them carefully apart, and numbered them by means of brass rings in their ears, and recorded the matings; therefore, the observations, so far as they go, I believe to be reliable, but I have not recorded in all cases the deaths of young ones, especially those which died before their characters could be accurately determined. The expense has been defrayed partly out of a grant made by the Committee of the Royal Society appointed to apportion the Government grant for scientific research, and I desire to express my sincere thanks to the Government and the Royal Society for the assistance thus given to me.

The experiments have been made with wild rabbits, white Angora rabbits, and Himalayan rabbits.

The wild rabbits are much more shy than the various varieties of tame rabbits, and for this reason the actual times of mating

could not be recorded. The wild rabbits live and breed quite happily in captivity provided they are allowed sufficient covert. They never appear in my cages in the daytime outside their hutch. I notice that the time of year when captivity seems to them most irksome is the late autumn. This is the time of year when we usually find rabbits lying out all day in the long tussocks of a grass field.

The original wild rabbits were obtained from Downham, in Lancashire, my father's home, now belonging to my brother. Downham, except for the village, is all grassland, woodland or moorland. The rabbits were taken from a burrow on the edge of the moor some two miles from the village in a part as far away as possible from places where I could recollect having ever seen black rabbits or rabbits in any way resembling tame breeds. I believe them to be as purely wild-bred as any rabbits in England are. The pair were brother and sister in all probability. This couple had two litters while in captivity in 1906 which were ordinary wild rabbits. Unfortunately the doe and the young ones eventually escaped, having bitten through the wire of their cage in 1908. She took up her abode, however, ten yards off her prison and gave birth to a third litter. These young ones were also all wild.

The litters under consideration are all of them the offspring of this one wild buck. The white Angoras were purchased as pure Angoras, and I had several litters by them all apparently pure white Angoras. The Himalayans were purchased from Mr. Wallis, of Cambridge, a well-known breeder of Himalayan rabbits, as pure Himalayans, and I had apparently pure-bred Himalayans from them. So I have no reason, *prima facie*, to believe that the rabbits with which I started were otherwise than pure-bred wild, white Angora, and Himalayan.

Breeding experiments on Mendelian lines with rabbits have been made by several men already, notably Hurst, 1905, Castle, 1903, 1905, 1907, Woods, F. A., 1903, but, so far as I know, none have been recorded of wild rabbits. The points which lend themselves to experiments of this nature are, of course, those characters in which the several breeds differ most from each

other. Some are obviously more easy to trace than others. Thus the character of the fur, whether short like the wild rabbit's fur, or long like that of the Angora, is an excellent character. Colour is also good, but the general colour of a wild rabbit is due to several colours, so that the character, though good, is a more complex one to follow. On the other hand, characters such as the wildness of the wild rabbit is far more difficult to follow, since familiarity breeds contempt to a certain extent even when the wild trait is evident in the young. In these preliminary and very incomplete observations the characters which have been recorded are:

1. Short or long hair.
2. Colour of coat.
3. Markings on coat.
4. Size.
5. Wildness.
6. Weight.

WILD RABBIT CROSSED WITH WHITE ANGORA.

When a wild rabbit buck is crossed with a white Angora doe the offspring are all closely like the wild buck. This is a case of dominance, the wild colour and short hair being dominant over the white and long fur of the Angora. They are small like the wild rabbit. Thus in 1909 the buck wild rabbit weighed 3 lbs. 5 oz. The average weight of white Angora is about 5 lbs. The F 1 wild white Angora weigh on an average 3 lbs. 7 ozs. In size, too, we find that the F 1 generation are more like their wild father than the Angora mother.

Thus, the wild measures 1 ft. 8½ ins. from the nasal septum to the tip of the tail over the head and along the back bone. The Angoras measure 1 ft. 11 ins., the hybrids 1 ft. 8½ ins. The wildness of the hybrid F 1 is well marked, but it is very difficult to estimate, but, though more shy than the tame mother, the young are not as shy as the wild father. I should be inclined to regard the condition as intermediate; for the young of the hybrid are not nearly as shy as the young of the pure-bred wild parents

So we are led to conclude that in the hybrid generation F 1 of wild and white Angora—at least when the buck is wild and

the doe Angora—the individuals are all like one another, but are much more like the wild parent than the Angora parent; in fact, as regards the colour and length of the fur, size and weight they might be mistaken for wild rabbits. That is to say, the wild is dominant over the Angora in all these characters. But as regards the psychical character of wildness the influence of the wild parent is less marked. But this dominance is not, even with respect to colour, an absolute dominance. Moreover, the degree of dominance varies with the mother. I bred the wild rabbit father with several white Angora does, and although each individual of a family is like its brothers and sisters, yet the families are usually distinguishable. Thus, one family will have a yellower general tint than another; or lighter marks occur, sometimes as a pair of lighter lines running fore and aft along the sides. But, speaking roughly, the dominance of the wild is very well marked in all characters mentioned except wildness.

I have had altogether six families of F 1 hybrids from this wild buck and five white Angora does. Thirteen young were produced which survived till adult life, two died before maturity, besides an unknown quantity which died quite young.

In this table No. 1 is a wild buck, and Nos. 3, 8, 12, 13, and 35 are white Angora does.

No. 1 ♂ × No. 3	$\left\{ \begin{array}{l} \text{No. 16 ♀} \\ \text{No. 17 ♂} \\ \text{No. 18 ♂} \\ \text{No. 19 ♀} \end{array} \right.$	All these are closely like the wild father in fur, colour, markings, size, and weight.
No. 1 ♂ × No. 8	$\left\{ \begin{array}{l} \text{—} \\ \text{—} \end{array} \right.$	
	died young	
No. 1 × No. 12	$\left\{ \begin{array}{l} \text{No. 23 ♂} \\ \text{No. 24 ♀} \\ \text{No. 25 ♂} \\ \text{.. ?} \end{array} \right.$	
No. 1 × No. 35	$\left\{ \begin{array}{l} \text{No. 54 ♂} \\ \text{No. 55 ♀} \\ \text{No. 56 ♀} \end{array} \right.$	
No. 1 × No. 13	$\left\{ \begin{array}{l} \text{No. 51 ♀} \\ \text{No. 52 ♀} \\ \text{No. 53 ♀} \end{array} \right.$	
No. 1 × No. 3	$\left\{ \begin{array}{l} \text{No. 110 ♀} \\ \text{No. 111 ♀} \end{array} \right.$	

Several crossings between the hybrids have been made giving the following individuals of the F₂ generation.

No. 16 × No. 13, a litter, all died very young.

No. 16 × No. 17, a litter, all died very young.

No. 19 × No. 18.	No. α, white, long Angora fur	} All died 10 weeks old.
	No. β, grey, short fur	
	No. γ, grey, short fur	
	No. δ, grey, long Angora	
	No. ε, grey, long Angora	

No. 19 had a litter by a wild rabbit, all the offspring being wild colour, darker, I thought, than the wild colour of the hybrid generation.

No. 19 × No. 18. No. 64 ♂ grey, short fur.
 No. 65 ♀ white, short fur.
 No. 66 ♀ grey, short fur.
 No. ζ (short blue coat, died 10 days old.

No. 19 × No. 18. No. η grey, short fur.
 No. θ grey, short fur.
 No. ι grey, short fur.
 No. κ grey, short fur.
 No. 71 grey, short fur.
 No. 70 grey, long Angora.

No. 24 × No. 25. No. χ black, long Angora fur (died 4 weeks old).
 No. ψ black, long Angora fur.
 No. λ white, long Angora fur.
 No. μ grey, short fur (died).
 No. ν grey, short fur, yellower than normal.

No. 56 × No. 54 or 55.

Four young were born. All apparently alike and apparently wild, and for some weeks there was no suggestion of the long coat of the Angora type.

When a month old two became long-haired.

No. ξ grey, long fur (died 6 weeks).

No. 67 grey, long fur.

No. 63 grey, short fur.

No. 69 grey, short fur.

No. 51 \times No. 53.

No. 52 \times No. 53.

} These two families were mixed.

No. σ grey, short fur.

No. π grey, short fur.

No. ρ grey, short fur.

No. σ grey, short fur.

No. τ white, short fur.

A black and the grey escaped too young to show character of hair.

So of the F₂ generation of wild and Angora cross I have records of 28 individuals. More were born, but either they died so young as to be indeterminable, or I have no record.

Hurst's experiments with the Belgian hare and Angora gave *several types with Dutch marking*. Thus, although the Belgian hare is similar in colour to the wild rabbit, except that it is yellower, yet there is evidently a marked difference in the composition. The *wild and Angora cross* has never so far given a rabbit with any trace of Dutch marking.*

Interesting combinations are obtained by mating the hybrid F₁ individual with the recessive mother (white Angora).

Thus No. 18 σ \times No. 3, that is 18's mother, gave—

No. 20 —, white Angora.

No. 21 —, white Angora.

No. 22 —, blue, short hair?

No. ν —, black (died young).

Again, a second litter :

No. 26 φ , white Angora.

No. 27 σ , white Angora.

No. 28 σ , white Angora.

No. 29 σ , blue, short.

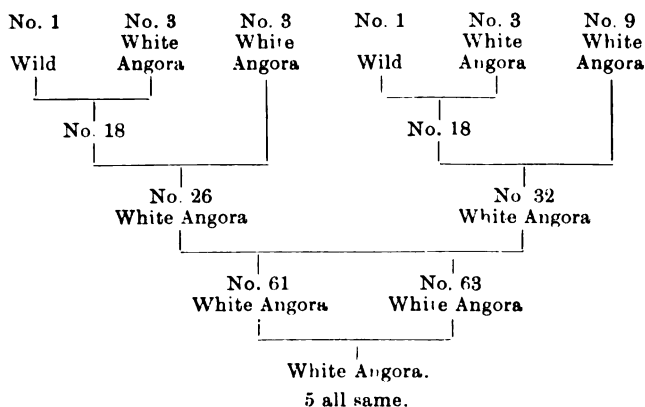
No. 30 φ , black Angora.

No. ϕ —, wild, long (died).

* The difference might be in the Angoras used. An Angora in the absence of pigment might have the factor for pattern without showing it.

Since both the white colour and the long hair are recessive to the wild colour and short hair, then, whenever they turn up in combination, the individual must be a homozygote for those characters, and should, if bred with a similar one, give only white Angoras.

The probability of this being true is shown in the following tables:—



The five white Angoras are, however, much smaller than their great-grandmothers. The size does not seem to follow the Mendel law, but the size seems to become lost, so that No. 63 weighs no more than No. 1, and 1 lb. 5 ozs. less than No. 3, or 1 lb. 9 ozs. less than No. 9.

May it be that the size of the Angora is not really a heritable quality in the Mendelian sense? That is to say, in the definition given above the quality is of the nature of a fluctuation rather than a mutation. Just as a plant which develops in a particularly suitable soil may evince certain characters which only remain so long as the individuals are grown under the same conditions, so size of the Angora rabbit when crossed with the wild rabbit is not retained from generation to generation because the environment of development, when shared with the wild gametes, is not congenial, and so the fluctuation due to particular conditions (co-partnership with another white Angora gamete) is lost.

The numbers are not sufficient to calculate the ratio of occurrence of the several types, which for the F 2 generation are—
(i.) grey short fur, (ii.) grey long fur, (iii.) white short fur, (iv.) white long fur, (v.) black short fur, (vi.) black long fur, (vii.) blue short fur.

WILD AND HIMALAYAN.

The Himalayan rabbit is a small white rabbit with short hair, with the ears, tail, paws and nose black. The hair of the toes is yellow. Weight, about 3 lbs. 10 ozs.

I had two does and one buck. Each doe bred with the buck Himalayan gave typical Himalayans.

I crossed each doe with the wild buck No. 1. In one case I obtained for the hybrid F 1 generation all similar individuals bearing generally the characters of the wild buck. That is to say, they were wild colour, with no special markings which distinguished the ears, feet, tail, etc. Nevertheless, they were not quite like the hybrid, wild and Angora. They have a kind of irregular pattern of darker hair.

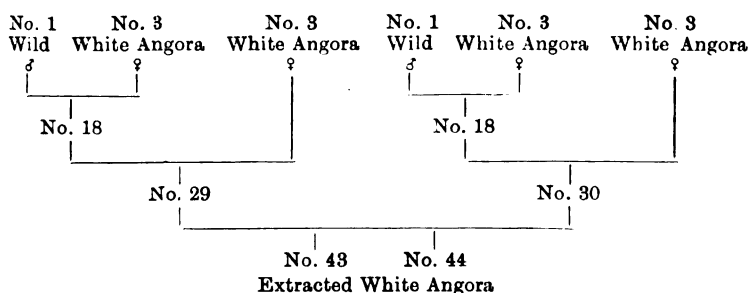
When the buck was crossed with the other Himalayan doe the surprising result was that some were like the hybrids of the other pairing, but some were what one would ordinarily call black, but they were of a very different type of blackness from the blacks which turned up among the Angora crosses. The fur was not made up of black hair alone, but of black and deep reddish yellow hairs. The fur is quite short like that of a wild or Himalayan. A wild rabbit has certain hairs which are spear-shaped, that is to say, they have a thicker flattened part just short of the tip. These hastate hairs are black at the tip and below the flattened spear-head they are also black, but the spear head is yellow. These hairs stand out farther than the short cylindrical ones, the two kinds forming the over-hair and fur respectively. The fur covers the whole body pretty evenly, but the over-hair is more abundant on the dorsal surface, and is absent from parts of the legs, and is very sparse on the ventral surface. These hairs in the black type of hybrid between wild and Himalayan remain, to some extent, unpigmented in the

spear-head, and so give the black a mottled appearance characteristic of the wild type. This seems to show that the Himalayan doe was not homozygous. Either she or the wild male must be heterozygous, but as this buck has been mated with six other does, five being Angoras, one a Himalayan, and nothing comparable occurred in any, even the Himalayan, we may suppose that the doe Himalayan in question is the heterozygous member.

I have bred the blacks together, and have crossed the blacks with white Angoras pure bred, and with a heterozygous wild and white Angora. In all cases white Himalayans as well as black (probably) may be produced as follows:—

The black hybrid (wild with Himalayan) bred together gave two litters, but the first died quite young. The second family consisted of four individuals, two black like the parents, one black with a white streak on the face, and one white Himalayan. A third litter gave two grey (wild) and one black; a fourth, two blacks.

I crossed the curious black type of wild and Himalayan hybrid with some extracted white Angoras with the following results:



No. 43 × Himalayan Black Hybrid. No. 44 × Himalayan Black Hybrid.

No. 73 ♂ black glossy short fur, developed orange patches after one year

No. — black

No. 74 black ♂ with yellow hairs

No. — black

No. 75 white Himalayan ♀, but lighter colour in points

No. — white

No. 76 black glossy ♀ short fur

No. — white, died?

No. 77 ordinary black ♀ short fur

No. ω died young, white

A black hybrid doe (wild by Himalayan) mated with a blue hybrid buck (wild by white Angora) (No. 29) gave a litter consisting of two white Himalayans, one black, one wild.

In these three latter breedings the apparent white Himalayans are no doubt heterozygous combinations with white Angora, the Himalayan being epistatic (dominant) over the white Angora.

Himalayan mated with white Angora gives two types for the F 1 generation. These hybrids are Himalayan-like, having short fur and marking like the Himalayan, but usually the black points are made much lighter than they should be by the presence of white hairs. In the other type the black points are much darker. I have had only one litter of F 2 generation from these Himalayan by white Angora crosses. In this the four individuals were all like the Himalayan at six weeks old, when they died. The parents were one of each type, the dark and light Himalayan by white Angora hybrids.

Another question of practical interest is the degree of faithfulness which the Mendelian law exhibits. I mean, when we say that according to this law the homozygous individuals of the F 2 or later generations are like their respective pure-bred grandparents or more distant ancestor, do we really mean that they are exactly alike?

For instance, in the case just described are the extracted white Angoras facsimiles of their white Angora fore-bear? Are the extracted Himalayans got by crossing the wild coloured hybrid with the Himalayan mother a facsimile of her? One must answer yes, in so far that the rabbit, in the one case, is undoubtedly a white Angora rabbit, and, in the other case, undoubtedly a Himalayan; but also no, in that they are very bad white Angoras, and very bad Himalayans.* The white Angoras have lost much of their characteristic weight and size and length of hair. The Himalayans are badly marked, the ears have white fur in parts, there are black specks on the body. This falling

* As regards these Himalayans, there has been such a marked improvement since this was written three months ago that the case must be dropped. There remains the inferior Angora and the loss of colour in the Belgian hare recorded by Hurst [v. Bateson, p. 119].

below the standard is no doubt an example of the correctness of Bateson's view that we are dealing with detail that comes within the definition of fluctuational variation given in an earlier part of this paper. Thus the points which tell in the show ring may very likely be outside what can be effected by Mendelian principles of breeding alone. For generations in the pure strain of Angora rabbits the gametes have been moulded and the embryos developed in a particular environment, and are carefully guarded from any internal disturbing influences. The prize strain is maintained by this special treatment as a well-marked fluctuation at a point eccentric from the normal.

If we but once compel the life-line to swerve into a new environment, though but for one cycle, as we do when we force an Angora gamete to enter into co-partnership with the gamete of the wild or other breed, we are probably doing as much harm as the gardener who fails for one summer to cut his lawn, so that when, on segregation, the life-line breaks with its alien partner and is again allowed to follow along in its congenial environment by being coupled with a pure Angora gamete, we need not be surprised that it has suffered, and that the desired fluctuation is not perhaps as marked as it was before.

This loss of character by unsuitable companionship is, in itself, an interesting feature and difficult to estimate.

I think the following list of weights and sizes is of some interest. The Angora with Himalayan strain is not as good after its adventure with the wild rabbit as before (I am speaking, of course, of the whole life-line, not of the individual; I am not for one moment arguing about telegony, to which, by the way, my breeding experiments, so far as they have gone, give not one atom of support), but it is difficult to say, especially in the case of the Angora, what exactly the deterioration consists of. The weight, however, is a fairly well-marked character and can be accurately recorded. I have given the weights and lengths of animals with which I have been dealing. The length is obviously less accurate than the weight. The length was obtained by measuring by tape measure from the nasal septum to the tip of the final vertebra of the tail, by passing

the tape over the head, following the fold of the neck, and so along the backbone to the distal end of the tail.

The ages, so far as I knew them, are given. All the rabbits thus recorded are one year and over.

No doubt the age has a very considerable effect upon the weight even after one year old; but the differences of the weight of the several breeds is sufficiently well marked, and make the records of interest after full allowance has been made for the difference of age.

Then, again, a doe which has given birth to several litters in the season becomes abnormally poor in condition and loses weight, *e.g.*, No. 3 in table below.

		Description of Rabbit.	Age in 1909.	Weight, 1909.	Size.	Weight, 1910.
				lbs. ozs.	ft. ins.	lbs. ozs.
P	No. 1	Wild buck	4 years ...	3 5	1 8½	3 3½
P	No. 4	White Angora ♂	4 years ?	5 3	1 11	5 1
P	No. 36	White Angora ♂	3 years ?	5 15	1 11	5 11
P	No. 3	White Angora ♀	4 years ?	4 6	1 10	3 14
P	No. 9	White Angora ♀	4 years ?	4 10	1 11	4 1
F 1	No. 18	Hybrid, wild × w Angora ♂	3 years ...	4 3	1 10	4 3
F 1	No. 23	Hybrid, wild × w Angora ♂	2 years ...	4 0	1 9	3 12
F 1	No. 53	Hybrid, wild × w Angora ♂	1 year ...	3 6	1 8	3 6
F 1	No. 55	Hybrid, wild × w Angora ♂	1 year ...	3 4		
F 1	No. 19	Hybrid, wild × w Angora ♀	3 years ...	3 8		
F 1	No. 51	Hybrid, wild × w Angora ♀	1 year ...	3 7		
F 1	No. 52	Hybrid, wild × w Angora ♀	1 year ...	3 5	1 8	3 4
F 1	No. 56	Hybrid, wild × w Angora ♀	1 year ...	3 6	1 8	
F 2	No. 31	Extracted white Angora ♂	1 year ...			
F 3	No. 63	Extracted white Angora ♂	1 year ...	3 1		
F 2	No. 32	Extracted white Angora ♀	2 years ...	3 9		
F 3	No. 43	Extracted white Angora ♀	2 years ...	3 9	...	3 11
F 3	No. 44	Extracted white Angora ♀	2 years ...	3 10		
F 3	No. 61	Extracted white Angora ♀	1 year ...	3 8		
	No. 75	Pure Himalayan	3 6		
	No. 59	Pure Himalayan ♂	2 years ?	3 10	...	3 7
	No. 60	Pure Himalayan ♀	3 years ?	4 0		
	No. 72	Pure Himalayan ♂	3 14	...	3 11
F 1	No. 38	Hybrid Himalayan wild (black)	× 2 years ...	3 3		
F 1	No. 57	Hybrid Himalayan wild (wild col.)	× 11 months	2 10	...	2 14
F 1	No. 58	Hybrid Himalayan wild (wild col.)	× ...	2 14		

CONCLUSION.

A man who is an artist by nature may, without much knowledge of pigments, produce an impression which contains the essence of a picture, but it will be an unfinished production. To convert that sketch into a finished work of the highest order requires a skilfulness and knowledge of technique to which only a few ever attain. So the man of science, by his appreciation of the laws of inheritance and variation, especially by that connected with the name of Mendel, can produce with rapidity and certainty many interesting combinations of characters, but there is still, probably, work left for the old-world fancier who by a technique or methods extremely difficult to analyse, and who is probably dealing to a large extent with the fluctuational type of variability, is able to reach and maintain a high order of finish, in fact, to perfect in fur or feather what Nature, by the composition of the gametes, has suggested to him in a rough and sketchy form.

The recognition that certain variable characters are, to an appreciable extent, due to fluctuation, and are not solely due to factors guided by Mendelian principles, is a matter which is of special importance to medical men, educationalists, and all interested in the welfare of society.

Professor Punnett, on page 81 of his book on Mendelism, writes "education is to man what manure is to the pea. The educated are in themselves the better for it, but this experience will alter not one jot the irrevocable nature of their offspring. Permanent progress is a question of breeding rather than of pedagogics; a matter of gametes, not of training. As our knowledge of heredity clears, and the mists of superstition are dispelled, there grows upon us with ever-increasing and relentless force the conviction that the creature is not made but born."

This view, no doubt, is to a large extent a true one, but does it represent the whole truth? If so coarse a character as the weight of an Angora rabbit or the colour of the Belgian hare (Hurst v. Bateson, p. 119) can be altered by the change in environment through even one cycle of bad co-partnership,

we may well doubt whether the subtle qualities which distinguish the good from the vicious, the successful man from the wastrel, may not suffer through lack of a fluctuational influence. And we may even venture to predict that the great philanthropist or statesman of the future will be he who, in his attempt to control the destiny of the human race, sees in education, although its influences may be of the fluctuational kind, a superstructure that is as essential to the finished man as the gametic foundation on which it stands; and the successful nation of the future will be that which neglects neither gamete nor gamin.

The following is a list of the more important works on this subject printed in English. For a list of books and papers in foreign languages and the general literature of the subject the reader is referred to the bibliography given by Mr. Bateson in his own work quoted below.

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A CASE OF ACUTE FATAL STAPHYLOCOCCAL SEPTICÆMIA.

By

HERBERT FRENCH, M.D., F.R.C.P.

CASES of acute fatal septicæmia due to staphylococci are probably much rarer than similar cases due to other micro-organisms, particularly streptococci and pneumococci. Nevertheless, from time to time one meets with very virulent staphylococcal infection. One is familiar with the fatal effects that are apt to ensue when this organism attacks bones or joints—acute staphylococcal periostitis, acute staphylococcal osteo-myelitis and acute staphylococcal arthritis. One is, perhaps, less familiar with acute staphylococcal septicæmia running a rapid and fatal course and resulting from superficial infection of the skin or from a whitlow. When a whitlow or other similar septic focus leads to fatal septicæmia, one is, *a priori*, a little inclined to think that there must have been a streptococcal rather than a staphylococcal infection, but that staphylococci may themselves produce fatal septicæmia has been well established by bacteriologists of recent years, and the following is a case in point:—

Mary C., æt. 33, was admitted into Miriam Ward, Guy's Hospital, on June 21st, 1909, and died upon June 22nd, 1909. She came in for hyperpyrexia and extreme drowsiness. She gave the history that she was a married woman who had a child three months old, born without any difficulty, the puer-

perium being absolutely normal. She herself had been perfectly well until one day before her admission, that is to say, until June 20th, when in the afternoon, without apparent cause, she had a severe rigor. The following day, June 21st, she vomited and felt decidedly unwell, and about 5 o'clock in the afternoon she walked to the hospital from Crosby Row. She was found to be very drowsy, with a temperature of 105° F. She was sweating about her scalp and forehead, but not about her body generally. No abnormal physical signs could be found in the heart, lungs or abdomen. There was a septic place upon the left thumb, apparently a whitlow, which she herself had opened with a knitting-needle, expecting to find matter in it, but no pus had come away. The temperature fell after admission to 103° F. The patient became comatose, and passed three motions unconsciously. She did not micturate. A slight vaginal discharge was noted; this was cultivated, and many organisms were found, including the bacillus coli communis, but no gonococci. The urine was drawn off by catheter, and was found to contain 0.5 parts of albumin per 1,000, together with one or two epithelial casts, but no blood and no sugar. The diagnosis was not at all clear beyond the fact that the patient was suffering from an extreme degree of toxæmia. The optic discs were normal and the nerve reflexes were natural, so that an intracranial abscess or meningitis seemed out of the question. By the morning of June 22nd the patient was completely comatose. The spleen, unpalpable the day before, was now to be felt, and Widal's reaction was tested, the result being indefinite. Blood cultures were taken by Dr. Eyre from the right median basilic vein, but before the result of the culture from this could be reported the patient died at 8.15 p.m. The temperature on June 21st was 105° F. in the Front Surgery, but 102.2° F. in the ward. The pulse rate was 140, and the respiration rate 28. On the morning of June 22nd the temperature was 103° F., the pulse rate 140, respiration rate 26, whilst at 6 p.m. the temperature was 103° F., the pulse rate over 150, and the respiration rate 32.

The post-mortem examination was made next day, and it revealed no definite macroscopic cause of death. There was no obvious uterine or other pelvic sepsis, and the viscera in general presented only such changes as were to be expected in any case of bacterial toxæmia with hyperpyrexia. The heart was flabby, the kidneys had some slight cloudy swelling of the epithelium, and the liver was enlarged and pallid from cloudy swelling and fatty change. There were subpleural and subpericardial petechiæ. Cultivations were taken from the heart blood, from the spleen and from the pericardium, and the chief interest of the case arose from the fact that all these post-mortem cultures, as well as those made from the blood from the median basilic vein during life, gave pure growths of *staphylococcus aureus*.

The case was one of acute and fatal staphylococcal septicæmia, and the source of the infection was, so far as could be judged, the septic focus upon the left thumb.

A CASE OF PRIMARY SARCOMA OF THE LUNG.

By

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AND

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ARTHUR RICHES, æt. 20, a clerk, had had pleurisy on the left side in 1904, and pneumonia in 1909, from both of which he made a complete recovery. His family history was good. In September, 1909, he began to suffer from attacks of acute pain in the left side of the chest behind. He was admitted on October 5th, 1909, under Dr. Hale White. On examination the left side of the chest was found to move badly, and measured a quarter of an inch less than the right. There was complete dulness and absence of tactile vocal fremitus over the left chest as high as the spine of the scapula. The voice sounds were diminished, and no breath sounds were audible at the left base. The heart could be felt pulsating to the right of the sternum. His face was pale rather than cyanosed; there were no dilated veins, no œdema of chest or arm, and no clubbing of the fingers. On October 6th a needle was inserted in four places into the left pleural cavity, but no fluid was found. On October 7th an X-ray photograph by Dr. Jordan showed that the lower two-thirds of the left chest were quite opaque, the dark area ending abruptly. The heart was considerably displaced to the right. The appearance suggested a pleural effusion, except that the limiting line above was too horizontal and too well defined. On

October 11th the chest was again explored with negative result. A blood-count showed 19,000 leucocytes. A diagnosis of intrathoracic growth was made. On October 29th the patient, who had become very depressed and emotional, left the hospital. On November 17th he was readmitted. He had lost four pounds of weight in four weeks, and now weighed 7 st. 8 lbs. He had had no pain or discomfort, and complained only of general weakness. He had little cough, and brought up only a little frothy sputum. His condition remained unchanged until the end of January, 1910, when he began to suffer pain on the left side, which steadily increased till his death on February 14th. For the last week he was only kept quiet by large doses of morphia. His temperature throughout was irregularly raised, alternating between 97° F. and 102° F. The pulse and respiration showed little change during the illness, averaging 110 and 30 respectively. There was never any hæmoptysis.

At the autopsy the body was seen to be profoundly anæmic and wasted. On removal of the sternum with the adjoining costal cartilages, the lower lobe of the left lung was seen to be almost entirely replaced by a huge mass of white growth. The upper lobe, which was compressed and airless, lay anteriorly behind the clavicle and upper two intercostal spaces. Only a thin strip of lung tissue remained from the lower lobe, and this was situated along the inner side of the mass. The heart and mediastinum were pushed far out to the right, so that they came to lie behind the right nipple. On removal of the viscera the growth was found to have replaced almost the whole lower lobe, leaving only a thin coating of compressed airless lung upon its inner and anterior aspect. This partial coating of lung tissue had a free edge, which could be raised from the lung all round, about one inch in width. On section, the growth was white and of the consistency of brain substance. In a few parts towards the centre it had begun to necrose. At the time it was thought that the growth had begun in the lung tissue, and had not merely extended into it, because the carbonaceous pigment could be seen extending far into its depth. The pleural

cavity was everywhere obliterated, but there were no dense adhesions and no tendency to invade or erode ribs. It was easily shelled out of the thorax. The upper lobe was small, airless and compressed, but not involved. The glands at the root of the lung were easily found, and were small and free from growth. The mass weighed 4,380 grms. and measured 10 inches in length and 8 inches across. There were no secondary deposits in any of the viscera. The opposite lung was œdematous, and the heart very small, flabby and wasted.

On histological examination the growth was seen to be a round-celled sarcoma. It was easy to identify both layers of pleura, with the obliterated pleural cavity, upon its surface. Far into the depth of the mass something of the alveolar structure of the lung could still be discerned. The bronchial glands were free from growth.

We have thought it worth while recording this case both because of the rarity of primary sarcoma of the lung, and because of the great size to which the growth attained. It weighed 4,380 grms. In 23 cases collected from the English, German and French literature none is recorded of anything approaching this bulk. Case 10 (3,095 grms.), Case 17 (1,800 grms.), Case 18 (2,300 grms.), and Case 20 (2,400 grms.), form the nearest approach.

Moreover, the physical signs and symptoms of the case during life were very characteristic of this rare condition. In contrast with growth of the mediastinal glands, and of growth spreading from the pulmonary root, these primary growths of the alveolar tissue of the lung seldom show signs of pressure. Œdema of chest and arm, cyanosis, dilatation of veins, inequality of pupils, and stridor, are all usually absent, as in the present case. If they do occur, they occur late, and are little marked, as in cases 15, 20, 21 and 22. In no other case were such signs met with. Secondary deposits are, on the whole, infrequent. In 11 cases there were no secondary deposits; in the others they were present, but were not numerous.

They were found in the various organs with the following frequency:—

Spleen	3
Spine	1
Pleura	1
Glands, Mediastinal and Bronchial	2
Cervical	3
Axillary	1
Heart	2
Kidney	1
Pericardium	1
Liver	1
Ribs	2
Brain	3

Presumably in not a few of these cases the infection was by direct contact and spread. That three cases should have developed hemiplegia from a cerebral deposit is remarkable, in view of the rarity of true metastasis. It suggests a comparison with the frequency of secondary suppuration in the brain in bronchiectasis and empyema, the so-called metastatic cerebral abscess.

In two cases, apparently primary, the growth was bilateral. Cases:—

Sex.—Fourteen were males, ten females.

Age.—

Years, 1—10	3
11—20	1
21—30	6
31—40	4
41—50	4
51—60	4
61—70	1

Hamoptysis was present in 11 cases, absent in 8, not mentioned in 5.

Heart.—The heart was displaced to the opposite side in 11 cases.

Pleural Effusion.—In one case alone was any large amount of fluid drawn off from the pleura during life. Twice it was present post-mortem, but only once in large amount. In one case with a large-bored needle actual sarcomatous tissue was withdrawn, and for that reason the author suggests the advisability of this procedure to aid diagnosis. In the case here recorded the sense of resistance and solidity, when the needle was thrust into the chest, was sufficiently marked to make the diagnosis certain.

Pyrexia.—In 10 cases pyrexia was present. In 3 cases it was absent. In the others it is not mentioned.

Sputum.—In no case was there anything characteristic in the sputum. It was never grass-green in colour, nor like red-currant jelly, although both these descriptions have been given as characteristic. One author records the finding of growth in the sputum in a case of *secondary* sarcoma of the lung. This is not recorded in any primary case. We have to thank Dr. Hale White, under whose care the patient was, for permission to publish this case.

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THE POST-MORTEM STATISTICS OF ULCERATIVE COLITIS AT GUY'S HOSPITAL FROM 1888 TO 1907.

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IN 1888, in the Guy's Hospital Reports, series iii., vol. xxx., Dr. Hale White called attention to a condition of ulceration of the colon which was not due to tuberculosis, to typhoid fever, or to malignant disease, and which he called simple ulcerative colitis. He says, "It is a disease occurring mostly in males, usually middle-aged. It generally lasts about two months; it is ushered in with attacks of abdominal pain; there is always diarrhoea; the motions are very fluid, but never dysenteric, often foul and having blood in them, which is not intimately mixed with the rest of the motion. The diarrhoea is liable to alternate with attacks of constipation, often there is vomiting. The usual course is for the patient soon to become sallow, to waste and become weaker and become collapsed, with a sub-normal temperature and with a feeble pulse, and finally to die. It may kill by perforation. It is sometimes associated with granular kidney." The truth of this description has not since

been seriously questioned, and was confirmed by a study of the cases which had occurred during the last twenty-five years in several of the large London hospitals, and which were recorded in order to provide data for a discussion upon ulcerative colitis at the Royal Society of Medicine. In this discussion, which is recorded in the Proceedings of the Royal Society of Medicine, vol. ii., Nos. 4 and 5, interest turned chiefly upon two points: the identity of ulcerative colitis with tropical dysentery; and the utility of such operative procedures as appendicostomy, cæcostomy or right-sided colotomy. In preparing the statistics from Guy's Hospital for this discussion we studied the Clinical and Post-mortem Reports from the years 1888 to 1907. In these records 97 cases were found in persons of adult age in whom the colon was found to show simple ulceration, that is, ulceration which was not tuberculous nor malignant, nor from typhoid fever. Of these cases, only 38 could be included in the statistics for the Royal Society of Medicine, for the reason that most of them occurred as a complication of severe disease, *e.g.*, of nephritis and of pyæmia, and it was thought misleading to include them in tables designed to show the symptomatology of so-called simple ulcerative colitis. It has been thought worth while now to publish the complete list of cases, because we think that they are not without bearing upon the two points of debate already mentioned—the identity with dysentery and the advisability of operative treatment.

These 97 cases can be divided at the outset into two groups:— 77 cases in which the ulceration was accompanied by and presumably secondary to grave and fatal disease elsewhere, and 20 cases in which the ulceration was the only lesion found post-mortem. The actual appearances in the colon found in these two groups were in no way distinctive, so that from an examination of the ulcerated area it would have been impossible in a given case to say whether it was or was not secondary to disease elsewhere. In a large number of the secondary cases ulceration was not suspected during life, but as will be seen later this was also true of a proportion of the primary cases.

77 CASES OF ULCERATION SECONDARY TO DISEASE ELSEWHERE.

1. A group in which the ulceration was due to the presence of virulent micro-organisms in the patient's blood.

JOHN C. (whose case is not included in the present statistics) was admitted in February, 1909, under Dr. Hale White, violently delirious, suffering from lobar pneumonia of eight days' standing. There had been no blood in the motions and no diarrhoea. At the autopsy, performed by one of us, there was consolidation in both lungs from lobar pneumonia. In addition, the cæcum and ascending colon were much congested, and the mucous membrane was covered by a thick greenish exudate. In places there was superficial ulceration of the surface. From the wall of the gut, from the blood, and from the mesenteric glands a mixed growth of b.c.c. and pneumococci was obtained.

Although proof is wanting, it seems reasonable to include the following cases in a group in which the ulceration may be due to the virulence of the specific micro-organisms of the primary infection:—

- a. 9 cases of puerperal septicæmia.
- b. 9 cases of infections of the urinary tract.
- c. 13 cases of pyæmia and septicæmia of various origin.
- d. 4 cases of malignant endocarditis.
- e. 2 cases of lobar pneumonia or pneumococcal septicæmia.
- f. 2 cases of glanders.

2. In a second group there is wanting evidence of any such virulent infection, but there was present an obvious cause for nutritional disturbance in the colon which may have served to render the gut more vulnerable.

- a. 4 cases with well-marked disease of the nervous system.
- b. 4 cases with well-marked congestion of the viscera from heart disease.

3. A third group may comprise cases in which there was present indubitable evidence of a chronic toxæmia.

- a. 15 cases of chronic nephritis, the majority of which had suffered from uræmia and many from terminal inflammatory complications.

b. 2 cases of severe anæmia, diagnosed as pernicious anæmia.

c. 1 case of diabetes.

d. 1 case of lead poisoning. A second case is included in the 15 which had chronic nephritis.

e. 1 case of pregnancy associated with uncontrollable vomiting.

4. There remains an indefinite group in which it appeared to us, both from the clinical history and the post-mortem appearances, that the ulceration must be regarded as secondary, although the evidence is less conclusive.

a. 6 cases, where an operation had been recently performed upon persons suffering from a suppurative condition elsewhere, or from the cachexia of malignant disease.

b. A miscellaneous group of 4 cases, in 2 of which there was suppuration in the female pelvic organs.

20 CASES IN WHICH THE ULCERATION OF THE COLON WAS THE ONLY LESION FOUND POST-MORTEM.

There remain 20 cases which are to be regarded as examples of that simple ulceration of the colon, to which Dr. Hale White was the first to draw attention. It becomes a question whether or not we are to regard these 20 cases as examples of an independent disease in which the colon is accidentally invaded by a specific micro-organism. That out of 97 cases of ulceration of the colon, no less than 77 should have occurred as secondary complications of disease elsewhere, in conditions of profound toxæmia due to an obvious cause, does not, of course, disprove the possibility, but it calls for proof of the existence of such a specific infecting agent in each case, and so far such proof has almost invariably been wanting. If, as has been shown, there is hardly any condition of profound toxæmia in which ulceration of the colon does not occasionally occur, in the absence of proof of the existence of a specific infection, verminous, amœbic, or bacterial, it would seem more reasonable to regard the ulceration of the colon as in all cases

expressive of a toxæmia the origin of which is sometimes clear, at other times obscure. To reason otherwise would be as illogical as to regard the simple purpura of children as a skin disease and to attempt its cure by local applications. A study of all the cases in which this simple ulceration of the colon occurs certainly suggests that the ulceration is in this sense secondary: the expression of the lowered resistance of the patient and the increased vulnerability of the intestinal wall. It does not suggest that the process by which the colon is infected is in any sense comparable to that found in tropical dysentery, where there is an invasion of the bowel by an organism too virulent for tissues, however well equipped, successfully to resist.

The evidence for this view may shortly be put as follows:—

1. As has been shown in a striking preponderance of cases, the ulceration is clearly secondary to some obvious cause.

2. In the minority of cases which are not thus clearly secondary, the history often suggests a similar conclusion. Many have suffered from a period of ill-health, more or less clearly defined, before the first symptoms pointing to disease of the colon have shown themselves. Thus, of the 20 cases which have been classed as of unknown origin, Case 7 had had previous hæmatemesis, Case 20 had had a gastric ulcer for three and a half years, and post-mortem an hour-glass contraction of the stomach was found. Cases 4 and 14 had had a painful multiple arthritis, described by the patients as chronic rheumatism, which had resisted treatment. Cases 11 and 12 were admittedly drunkards. Case 5 had been in a state of starvation for months.

3. The remarkable intermittency of the disease does not suggest a repeated invasion by a specific micro-organism. In this intermittency, in which a sudden relapse, followed often by slow and laborious improvement, may yet at any time overstep, as it were, the limits of recovery, it resembles in its clinical course other chronic intoxications, as, for example, uræmia, pernicious anæmia, gastric or duodenal ulceration.

It has, indeed, been suggested* that this terminal fulmination of the attack is due to the extension of ulceration from the lower to the upper segment of the colon, and that so long as the ulceration is confined to the lower part of the colon the fatal intoxication does not occur. Such a statement is, from its nature, difficult to prove or disprove. If it were true it would certainly imply that the disease was due to the local inoculation of a particular part of the bowel. If, on the other hand, the ulceration is the result of the lowered resistance of the tissues, we should expect the lesion to break out simultaneously over a wide area. Similarly in tuberculosis, with a lowering of resistance and a fall of the opsonic index, the final ulceration rapidly involves a wide extent of the alimentary canal, so that it is rare to find a single ulcer. Widespread tuberculous ulceration of the small intestine and ulceration of the larynx are apt to occur simultaneously. In all but one of the cases post-mortem the whole length of the colon was involved. In Case 5, however, it was the opinion of the demonstrator that the ulceration in the cæcum was old and the rest recent. In Case 10 the process in the ascending colon showed evidence of cicatrisation. On the other hand, in Case 3, who died after an operation, and who was admitted delirious, with signs of severe intoxication, the ulceration was confined to the lowest part of the colon. In all the other cases the ulceration was general.

4. Although many organisms have been described as being present in ulcerative colitis, none has been found with sufficient frequency to suggest that it is the specific cause. On the other hand, there is often evidence from the opsonic index, or from the agglutination reaction, that the resistance of the patient is lowered to the *bacillus coli communis*.

5. In attempting to estimate the prognosis in simple ulcerative colitis, the symptoms of worst omen are those which are the result of the auto-intoxication. Where the temperature is high and delirium marked, recovery seldom takes place. In 15 cases which recovered, the temperature averaged 100·2°F.; in 15 which

* Hawkins, *B.M.J.*, 1909, vol. i., p. 767.

died, 102.5° F. In 16 cases from the London Hospital, all fatal, the average maximum temperature was 102.1° F. In University College, of 38 cases which recovered 31 had pyrexia which did not reach 100° F., or had a normal or subnormal temperature. Of 12 cases which died, all but one had pyrexia over 101 F. On the other hand, it would seem that the number of stools per diem does not give trustworthy evidence of the spread or decline of the process. In Cases 3, 6 and 7 blood was absent throughout, and diarrhoea occurred late or not at all. In this respect individual cases at different times showed great variations, and there were wide divergences between cases, both where recovery followed and in those which died.

These considerations, taken together, suggest that the ulceration in the colon is not the result of any accidental invasion by a specific micro-organism, but is due to the presence of some toxin of unknown origin, and to the weakness of the defences of the bowel wall. Flexner found that the toxin of dysentery, injected intravenously, caused ulceration of the colon. That the colon acts as an excretory organ is shown in mercurial and lead poisoning, and is suggested by the frequency of ulceration in uræmia. The ætiology of ulcerative colitis would thus be in keeping with the modern view of the ætiology in gastric and duodenal ulcers. In both the ulceration is at times secondary to well-marked toxæmia of known origin. Perry and Shaw* have collected a series of cases in which duodenal ulceration was a terminal event in other chronic septic infections. Multiple erosions and widespread ulceration of the gastric mucous membrane is found from time to time under similar conditions. Among the autopsies, performed by us, of 1909, acute and fatal ulceration of the stomach occurred twice in cases from the surgical wards, in a case of compound fracture of the femur and in a case of suppurative cholecystitis. In other cases the predisposing condition is obscure and the ulceration presents itself as the primary lesion. Yet, gastric ulcer does not occur among persons in good health. It is

* Perry and Shaw, *Disease of the Duodenum*, G.H.R., vol. xxxv., p. 187.

unknown among primitive peoples and rare in those who live a healthy out-of-door life. It is the product of deficient sanitation, of overwork, overcrowding, undue development. The most effective treatment is that which most rapidly restores the nutrition of the patient, the most ineffective that which is directed solely against the local manifestation. It is probable that the principles upon which the Lenhartz method and other methods of forced feeding in gastric ulceration rest might, with advantage, be transferred to this condition of ulceration in the colon. The ulceration is of the same nature. It differs only in the possibility and likelihood of secondary infection, and the further rapid absorption of toxins from the bowel. An examination of the temperature charts of the cases recorded suggests that the danger is not immediate so long as the case is apyrexial, or so long as the temperature does not rise above 100° F. In such cases the treatment should be by rest in bed and by a system of forced feeding. In the Guy's Hospital Gazette, H. Stott has recorded the successful treatment of a series of cases of the apyrexial type which were under the care of Dr. Hale White. These patients were given large quantities of soured milk to drink and an antiseptic cyllin by the mouth; with one exception they were all vaccinated with the bacillus coli communis. In addition great care was expended upon their diet. The diet in Case 4 is thus described: "His powers of digestion were tested successively with Benger's food, arrowroot, and brandy, eggs and thin bread and butter, whilst protein food was added in the form of Sanatogen, Plasmon, and minced chicken and meat. Within ten days he was taking augmented full diet, vegetables and the coarser parts of the food stuffs being alone eschewed. It was hoped that the oiling of his food residue would be achieved by the malt and oil which he took and also by the cream." His weight on admission was 9 stone 4 lbs. When it reached 11 stone 2 lbs. his motions finally became completely normal.

Where the original ulceration is complicated by rapid absorption of toxins from the bowel, with evident signs, not merely

of prostration, but of marked auto-intoxication, where there is marked delirium and high pyrexia, it would appear that such medical treatment alone is insufficient. In these cases the operation indicated is that of appendicostomy. It is logical to expect improvement in these symptoms of auto-intoxication from an operation which permits the frequent flushing of the bowel by an antiseptic solution. Pent-up discharges are thus liberated and the surface of the ulcers kept clean.

Appendicostomy is selected because the manipulations in its performance are of the simplest, and there is no subsequent operation necessary for its closure. For it is well to remember that even where appendicostomy achieves its purpose, and arrests the auto-intoxication and pyrexia, the patient may still show that increased susceptibility which is the initial cause of the disease. At the Royal Society of Medicine Mr. Makins referred to the great danger of secondary operations for closure of colotomies performed in ulcerative colitis. "He did not know why this was so, and he had no actual experience of the accident, but in his hospital several patients on whom an artificial anus was made for the relief of ulcerative colitis had died from peritoneal infection as a result of operations for their closure." The explanation must lie in the lowered resistance of the patient, which persists in spite of the improvement of the local symptoms, and renders dangerous the extensive manipulations necessary to close an artificial anus.

The post-mortem appearance of the gut in cases of ulceration which have died gradually with exhausting diarrhoea and profound prostration, and which have escaped a virulent terminal infection, is sometimes very striking. The gut shows no evidence of cicatrisation and repair. It is often reduced to the thinness of tissue paper, and so friable and brittle that it is sometimes impossible to remove it from the abdomen without causing perforation.

TABLE I.—77 Cases of Secondary Ulceration of the Colon.

PUERPERAL INFECTION—

1889. P.-m. 205.—Death took place 8 weeks after a miscarriage from which the patient herself dated the symptoms.
1892. P.-m. 205.—Died of pyæmia following a puerperal infection.
1893. P.-m. 285.—Had puerperal septicæmia after a miscarriage; there was some placenta adherent in the uterus.
1898. P.-m. 290.—Had been recently confined; the uterus was not examined.
1901. P.-m. 405.—Had a miscarriage with septicæmia.
1902. P.-m. 211.—Had recently been confined at full term; she died of general peritonitis.
1903. P.-m. 189.—Died of pyæmia after induction of labour.
1904. P.-m. 109.—Had puerperal septicæmia from retained fragments of placenta.
1906. P.-m. 474.—Died with acute endometritis and puerperal fever.

INFECTIONS OF THE URINARY TRACT—

1890. P.-m. 379.—Had cystitis, with phosphatic calculi in the bladder; suprapubic lithotomy was performed.
1899. P.-m. 331.—Had a calculous pyonephrosis for which nephrolithotomy was performed.
1899. P.-m. 359.—Had hydronephrosis from an impacted calculus in the ureter; there were caseous glands in different parts of the body.
1902. P.-m. 428.—Had a large phosphatic calculus in the left kidney.
1904. P.-m. 66.—Had urethral stricture, old consecutive nephritis, extravasation of urine, and ulceration round the rectum.
1904. P.-m. 271.—Had ascending secondary nephritis of unexplained origin.
1905. P.-M. 85.—Had suppurative pyelonephritis, with a bed-sore, septic bronchopneumonia, and general peritonitis.
1906. P.-m. 501.—Died of stricture of the urethra, with cystitis.
1906. P.-m. 586.—Died of cystitis and ascending pyelonephritis.

PYAEMIA, SEPTICAEMIA, &c.—

1891. P.-m. 118.—Had cellulitis of the neck, pyæmic abscesses in the thyroid gland and subcutaneous tissue of the back.
1892. P.-m. 309.—Had long had gout, and died of cellulitis in the leg.
1897. P.-m. 403.—Had pyæmia with suppurative pericarditis, and an old tuberculous affection of the hip.
1898. P.-m. 141.—Had pyæmia, with abscesses in the lungs.
1898. P.-m. 180.—Had cellulitis of the neck and septicæmia.
1898. P.-m. 181.—Had cellulitis of the hand, abscesses in the lung, and pyopneumothorax.
1898. P.-m. 401.—Had cellulitis of the abdominal wall, pyæmia and secondary peritonitis.
1899. P.-m. 12.—Had septicæmia following a radical cure for inguinal hernia.

1902. P.-m. 241.—Had appendicitis and general peritonitis; streptococci were found in the blood.
1902. P.-m. 514.—Had septicæmia and an acute sloughing vaginitis and general peritonitis; one ovary was large and inflamed; streptococci were found in the blood.
1903. P.-m. 14.—Had hydronephrosis and double ovarian cystic disease; cultivation from the blood gave a mixed growth; b.c.c. and staphylococci aureus.
1906. P.-m. 356.—Had hepatic and pulmonary abscesses; the pneumococcus was obtained from the pus.
1906. P.-m. 429.—Had pyæmia, with cellulitis of the scrotum and penis.

INFECTIVE ENDOCARDITIS—

1900. P.-m. 231.—Had infective endocarditis and acute glomerular nephritis.
1901. P.-m. 209.—Had infective endocarditis, jaundice with a sloughing prepuce and glans penis; in the blood was found proteus vulgaris.
1903. P.-m. 5.—Had infective endocarditis.
1906. P.-m. 442.—Had infective endocarditis, with thrombosed mesenteric and colic veins.

LOBAR PNEUMONIA—

1901. P.-m. 177.—Had lobar pneumonia.
1905. P.-m. 229.—Had pneumococcal septicæmia, with acute pneumococcal laryngitis and pharyngitis.

GLANDERS—

1898. P.-m. 115.—Had glanders with cellulitis of the scalp, and a pustular eruption and foci in the lungs.
1900. P.-m. 290.—Had glanders.

DIABETES—

1888. P.-m. 150.—Had diabetes of long standing, with diabetic cataract; the gall bladder was inflamed and sloughing, and contained many calculi.

PERNICIOUS ANAEMIA—

1902. P.-m. 83.—Died of pernicious anæmia.
1903. P.-m. 258.—Died of pernicious anæmia.

PREGNANCY—

1891. P.-m. 136.—Occurred during a pregnancy marked by much severe vomiting.

WITH DISEASE OF THE NERVOUS SYSTEM—

1890. P.-m. 283.—Had injured his spine 18 days before death; it was a depressed fracture of the third lumbar vertebræ.
1894. P.-m. 223.—Had long had tabes dorsalis.
1897. P.-m. 100.—Had hemiplegia from syphilitic cerebral endarteritis; there was terminal hypostatic pneumonia.
1907. P.-m. 537.—Had softening of the spinal cord, suppurative nephritis and jaundice.

WITH CARDIAC CONGESTION—

1892. P.-m. 460.—Died of heart failure with mitral and aortic disease; there was marked venous congestion of the viscera.
1894. P.-m. 163.—Died of heart failure, with early granular kidneys.
1904. P.-m. 204.—Had aortic and mitral disease, tricuspid regurgitation, jaundice and anasarca, with acute pleurisy and perisplenitis.
1907. P.-m. 129.—Had mitral regurgitation with cardiac failure, and great venous congestion of the viscera.

NEPHRITIS—

1888. P.-m. 84.—Had well-marked lardaceous disease of the kidney, liver and ileum; chronic interstitial nephritis and cirrhosis of the liver; in the spleen there were scattered fibrous patches, which were thought to be gummatous.
1888. P.-m. 289.—The kidneys showed chronic interstitial nephritis; he had long had lead poisoning, with wrist-drop.
1888. P.-m. 300.—The kidneys showed chronic interstitial nephritis; he had suffered from gout, headache and œdema.
1888. P.-m. 419.—The kidneys showed chronic interstitial nephritis; there was profound wasting and anæmia, and a terminal acute peritonitis.
1889. P.-m. 278.—Death was due to chronic nephritis in an alcoholic subject; there was a terminal septic bronchopneumonia.
1898. P.-m. 250.—Had chronic interstitial nephritis with uræmia.
1899. P.-m. 361.—Had chronic interstitial nephritis with anasarca.
1900. P.-m. 304.—Had granular kidneys, and suppurative parotitis on the left side.
1901. P.-m. 42.—Had chronic interstitial nephritis and adherent pericardium.
1904. P.-m. 53.—Had chronic interstitial nephritis.
1905. P.-m. 8.—Had chronic interstitial nephritis.
1905. P.-m. 593.—Had uræmia, albuminuric retinitis, chronic interstitial nephritis, with a long history of gout.
1906. P.-m. 80.—Had acute on chronic nephritis with œdema.
1906. P.-m. 129.—Had chronic interstitial nephritis with uræmic coma: the kidneys together weighed 82 grammes.
1907. P.-m. 615.—Had chronic interstitial nephritis with uræmic coma.

LEAD POISONING—

1897. P.-m. 138.—Had long suffered from lead poisoning, with colic and blue line upon gums; he had had syphilis; and for 18 months there had been ulceration about the right elbow and thigh. See also Nephritis, 1888, P.-m. 289.

AFTER OPERATIVE INTERFERENCE—

1899. P.-m. 329.—Had a hysterectomy performed, and died of general peritonitis.
1900. P.-m. 42.—Had been admitted for carcinoma of the breast, which had been amputated; she died of septic bronchopneumonia.

1900. P.-m. 58.—Had carcinoma of the rectum for which colotomy had been performed.
 1901. P.-m. 5.—Had undergone operation for ectopic gestation.
 1904. P.-m. 246.—Had general peritonitis after hysterectomy.
 1906. P.-m. 585.—Had had a foul uterine discharge for 15 months, for which hysterectomy had been performed; the wound was healthy.

SUPPURATIVE CONDITIONS OF FEMALE PELVIC ORGANS—

1888. P.-m. 172.—There was pelvic peritonitis and cellulitis with hydro-salpinx; there was old mitral and tricuspid stenosis; and scarred kidneys from an old gonorrhœal infection.
 1900. P.-m. 36.—Had an abscess of the broad ligament, for which she had recently undergone an operation.

MISCELLANEOUS—

1897. P.-m. 133.—Was admitted with a cut throat, and died with a septic bronchopneumonia.
 1898. P.-m. 179.—Had mitral stenosis with an ante-mortem thrombus in the heart; had embolism, with resulting gangrene of the leg.

TABLE II.—Twenty Cases in which Ulceration of the Colon was the only Lesion found after Death.

1889. Case 1. P.-m. 133.—Ruth C., æt. 23. Admitted 27th March for diarrhœa and melæna. She had passed blood in her stools six weeks before admission, and had had constant diarrhœa ever since. On admission she was much exhausted, and was passing bright red blood in her stools; vomiting was frequent; continuing to pass large motions of blood, she died of exhaustion three days after admission.

Post-mortem.—The large intestine was one continuous stretch of severe acute ulceration; the transverse colon was most affected, very little mucous membrane being left. The process was thought to have started in the transverse colon.

1890. Case 2. P.-m. 309.—Sarah W., æt. 25. Admitted for headache with diarrhœa and abdominal pain of a few days' duration. On admission the patient was languid, with a dirty tongue, and was passing two foul watery motions a day. The abdominal pain and diarrhœa continued. She grew thinner and feebler, with clammy skin. She first passed blood some three weeks after admission, and died soon after of exhaustion.

Post-mortem.—Extensive ulceration from the ileo-cæcal valve to the anus. Some of the ulcers were large, others smaller, such as might be formed by the destruction of the solitary follicles, from which it was supposed the ulcers had originated.

1891. Case 3. P.-m. 479.—Sarah S., æt. 50. Admitted for an irreducible femoral hernia. Thirteen years before the patient first had a femoral hernia which was mostly reducible. Recently it had grown larger, which, with two days' vomiting, had alarmed her. Her bowels had been quite regular. On admission she was delirious. The hernia was explored without result, and no obstruction was demonstrated. After the operation diarrhœa set in and delirium continued, and on the 17th day the patient died.

Post-mortem.—The whole large intestine was very friable and much congested. One foot above the anus were three small superficial ulcers, which perhaps originated in the solitary glands. At the anus and for some inches above it the mucous membrane was almost entirely destroyed by ulceration; the muscular coat and, in parts, the cellular tissue being destroyed.

1893. Case 4. P.-m. 442.—Alice P., æt. 19. Admitted for diarrhœa. Two years before patient had had typhoid, and twelve months before a painful arthritis. She had been too weak to go to work for a year, and three weeks before admission had a cold. Since the typhoid she had alternately been suffering with constipation and diarrhœa. On admission she had headache, dizziness, and was very pale and weak, with foul breath and tongue. The diarrhœa continued; she was slightly delirious, with a pulse averaging 160. A diagnosis of typhoid fever was suggested; and she gradually sank and died.

Post-mortem.—The entire large bowel from anus to ileo-cæcal valve, including the appendix, was involved in ulceration.

1894. Case 5. P.-m. 45.—W. C. W., æt. 45. Patient had been half starved for months. On January 2nd he was seized with severe pain in the hepatic region. He was feverish, cold and shivering until his admission three weeks later. He was constipated all this time, purgatives, however, on two occasions producing thin and watery stools. He sweated a great deal and vomited occasionally. On admission he was jaundiced and very feeble. Incision was made into a large hepatic abscess. He subsequently had diarrhœa with mucus and blood in the stools, until his death soon afterwards. The relation between the ulceration of the colon and the hepatic abscess is here doubtful.

Post-mortem.—In the cæcum, the walls of which were thickened, the mucous membrane was extensively ulcerated; this ulceration was very old. There was extensive acute superficial ulceration in the rest of the colon.

1895. Case 6. P.-m. 445.—Patient had had several similar attacks of constipation, headache, malaise, pyrexia, and pain in the right iliac region. He had been ill and constipated for four days before admission. On admission both typhoid and appendicitis were suggested as a diagnosis. He passed foul watery motions, and grew steadily weaker; his headache continued, and he

became restless and delirious. The considerable tympanites was not relieved by colopuncture, and he died. He never passed any blood or mucus in his stools.

Post-mortem.—General peritonitis was revealed; also ulceration of the colon from the anus to the ileo-cæcal valve, some ulcers being large and some small, the latter beginning in the solitary follicles.

1896. Case 7. P.-m. 12.—Alice B., æt. 32. Eight days before admission the patient had pain in the abdomen, and diarrhœa with bloody stools. There was a history of former hæmatemesis. The patient was anæmic and in a state of noisy delirium; she was constipated and vomited, the constipation continuing until death.

Post-mortem.—There was a large patch of congestion in the ascending colon, and several small superficial ulcers in the cæcum.

1897. Case 8. P.-m. 266.—Harry C., æt. 5. A fortnight before admission the child complained of abdominal pain, and passed blood in its stools, and was admitted into a surgical ward. On admission it was very ill, with sunken eyes and feeble pulse, and a generally tender abdomen; he became gradually weaker and died somewhat suddenly.

Post-mortem.—The entire colon from the ileo-cæcal valve onwards was much thickened and studded with large ulcers, which were covered with a false membrane.

1897. Case 9. P.-m. 347.—Fred. P., æt. 36. Six weeks before he had had severe diarrhœa, and was admitted into a fever hospital as a case of typhoid fever. On admission into Guy's he was extremely ill and emaciated, with a dirty tongue and foul pea-soup stools. He died on the sixth day after admission.

Post-mortem.—Extensive ulceration of the colon, most marked in the descending and transverse parts of the colon, but also present in the cæcum. Several ulcers had perforated, causing general peritonitis.

1898. Case 10. P.-m. 2.—Nellie C., æt. 17. For three months patient had passed blood in her stools. On admission it was thought that the cause was a fissured anus and the sphincter was stretched. Later, vomiting set in. Her tongue became very raw. Ten days after admission the abdomen was very tympanitic, the patient was very haggard and restless, throwing her arms about. General peritonitis was diagnosed and laparotomy performed with negative result. She became weaker and died.

Post-mortem.—The whole colon was ulcerated; in the ascending colon the process had gone on to cicatrization in places. The sigmoid colon and rectum were acutely inflamed.

1900. Case 11. P.-m. 77.—W. D. B., æt. 25. Patient was a hard drinker, being sometimes drunk five nights out of seven, and a "reckless liver." A week before admission he had diarrhœa and vomiting. He became delirious, and his doctor diagnosed typhoid fever. On admission he was delirious, and after passing 17 stools in twenty-four hours, died the day after admission.

Post-mortem.—The whole of the colon was extensively ulcerated, especially in its lower half. In the cæcum and ascending colon were numerous recent ulcers.

1900. Case 12. P.-m. 350.—John B., æt. 45. On the day of admission patient was suddenly taken ill and became unconscious. On admission he gave evidence of being a heavy drinker; he was drowsy, restless and delirious, and passed his motions under him. His diarrhœa continued, and the delirium necessitated his being removed to the strong room. He developed cystitis, became gradually weaker and died.

Post-mortem.—The cæcum and the entire colon were ulcerated.

1901. Case 13. P.-m. 421.—James W., æt. 25. Patient was suddenly taken ill with diarrhœa and rectal hæmorrhage; his bowels were opened twenty to thirty times a day, but after admission no blood was seen in the stools. He was thin and anæmic, and, becoming gradually weaker, died three weeks after the beginning of his illness.

Post-mortem.—The large intestine was inflamed throughout; the ulceration was quite superficial and confined to the follicles.

1903. Case 14. P.-m. 412.—Albert T., æt. 38. Patient had suffered from multiple arthritis six months before, and had never recovered from this. He was admitted for diarrhœa and the passage of blood. He vomited unceasingly, became thin and rapidly weaker, and died unconscious.

Post-mortem.—General peritonitis was found and complete ulceration of the colon.

1904. Case 15. P.-m. 270.—Mary H., æt. 19. Patient had had diarrhœa and passed blood for eight weeks when she was admitted on April 19th. On admission she was very wasted and anæmic; her abdomen was normal. Soon after admission her temperature rose, and she passed pus per rectum, and the possibility of an abscess having burst into the bowel, perhaps from the broad ligament, was discussed. She continued to pass fluid stools, and gradually grew worse. On May 27th a tumour was felt per rectum, but owing to the patient's condition operation was considered inadvisable. She grew gradually feebler, and died soon after.

Post-mortem.—There was extensive ulceration destroying two-thirds of the mucous membrane. There were two localised collections of pus in the peri-rectal connective tissue communicating with the rectum.

1906. Case 16. P.-m. 276.—Maud P., æt. 22. Patient, who had always been anæmic, had suffered with diarrhoea for a year. This had become very much worse in the last month. She had recently slept badly, had headache, and vomited. Her tongue was ulcerated, and she had sores round the lips. On admission, her temperature varied between 103°F. and normal. She grew progressively worse, and died a few weeks after admission.

Post-mortem.—The entire large intestine was extensively ulcerated, the smooth muscular coat being in parts exposed.

1906. Case 17. P.-m. 381.—Annie S., æt. 46. Seven months before admission patient had diarrhoea with blood in her motions. This had continued, with intervals of constipation. On admission she was extremely ill, with a running pulse. She became weaker, and died suddenly after hæmatemesis.

Post-mortem.—General suppurative peritonitis was found. Numerous ulcers were scattered over the colon; two of these had ulcerated.

1906. Case 18. P.-m. 453.—Esther H., æt. 19. Patient was admitted for diarrhoea with blood, and vomiting. For a time she made great improvement, and was up and about. The sigmoidoscope revealed ulceration of the sigmoid. After being in hospital for about two months she had a relapse with hæmorrhagic diarrhoea. She was again "sigmoidoscoped," but the sigmoidoscope perforated the gut, and she died of general peritonitis.

Post-mortem.—There was extensive ulceration from the middle of the rectum to the ileo-cæcal valve; there were also some healed ulcers.

1906. Case 19. P.-m. 454.—James F., æt. 54. Seven or eight years before the patient noticed that his bowels were becoming irregular. Four or five years before he had passed liquid motions with blood. One month before he had great difficulty in passing his motions, passing sometimes nothing, sometimes fluid stools with blood. To relieve a condition which was thought to be one of intestinal obstruction colotomy was performed immediately, but the patient gradually grew worse and died.

Post-mortem.—There was extensive ulceration throughout the colon, and a fibrous stricture just above the anus.

1907. Case 20. P.-m. 375.—Amy H., æt. 38. The patient first had abdominal pain six years before. This was sometimes accompanied by the passage of blood. Three and a half years before she had a gastric ulcer. She was admitted in April for the passage of blood; this proving untractable, in July appendicostomy was performed, and the colon washed out. After temporary improvement the patient became weaker and died.

Post-mortem.—The colon was ulcerated throughout. There was also an hour-glass stomach, with a healed gastric ulcer, and gangrene of the lung.

TABLE III.—All Cases, thirty-four in number, in which, after death, the Colon was found acutely inflamed, but not obviously ulcerated.

1888. Case 1. P.-m. 114.—A child of 2½ died of extensive burns. The mucous membrane of the colon is noted as swollen and infected.
- Case 2. P.-m. 227.—A case of chronic interstitial nephritis, with a syphilitic testicle and a scarred liver; had acute catarrhal colitis.
1890. Case 3. P.-m. 242.—Multiple pyæmic abscesses associated with acute colitis.
1892. Case 4. P.-m. 70.—With cystitis and pyuria; had hæmorrhagic colitis.
- Case 5. P.-m. 219.—With diabetic coma; had severe catarrhal colitis.
- Case 6. P.-m. 261.—With senile gangrene of the foot; had acute catarrhal colitis.
- Case 7. P.-m. 368.—With suppurating ovarian cyst and general peritonitis; had acute catarrhal colitis.
1895. Case 8. P.-m. 4.—With atrophy of kidney and ascending nephritis of unknown origin; had acute catarrhal colitis.
- Case 9. P.-m. 29.—With diabetes; had acute catarrhal colitis.
- Case 10. P.-m. 73.—With lobar pneumonia; had acute catarrhal colitis.
- Case 11. P.-m. 133.—With double calculous pyonephrosis; had acute catarrhal colitis.
- Case 12. P.-m. 414.—With cardiac failure from mitral disease and severe visceral congestion; had acute catarrhal colitis.
1897. Case 13. P.-m. 401.—With tubal nephritis; had hæmorrhagic colitis.
1898. Case 14. P.-m. 70.—With enlarged prostate and cystitis; had hæmorrhagic colitis.
1900. Case 15. P.-m. 242.—With left hemiplegia from cerebral tumour; had acute colitis with membranous exudation.
- Case 16. P.-m. 325.—With cirrhosis of the liver, adherent pericardium, and jaundice; had acute colitis with membranous exudation.
1901. Case 17. P.-m. 217.—With lobar pneumonia; had acute colitis with membranous exudation.
- Case 18. P.-m. 363.—After osteotomy; had acute colitis with membranous exudation.
1902. Case 19. P.-m. 204.—With lobar pneumonia; had follicular colitis.
- Case 20. P.-m. 290.—With cerebral softening; had acute hæmorrhagic colitis.

1903. Case 21. P.-m. 224.—With acute tubal nephritis and undiagnosed peritonitis; had acute colitis with membranous exudation. Cultivations from mesenteric and bronchial glands gave mixed growth of b.c.c. and streptococcus longus.
1904. Case 22. P.-m. 183.—With calculous hydronephrosis; had acute catarrhal colitis.
- Case 23. P.-m. 319.—With pyæmia from otitis media; had acute catarrhal colitis.
- Case 24. P.-m. 441.—With necrosis of femur; had acute catarrhal colitis.
- Case 25. P.-m. 487.—With chronic interstitial nephritis, uræmia and albuminuric retinitis; had acute catarrhal colitis.
- Case 26. P.-m. 492.—With septicæmia; had acute catarrhal colitis.
- Case 27. P.-m. 501.—With kidneys "pale and cystic"; had hæmorrhagic colitis.
1905. Case 28. P.-m. 309.—With septicæmia from middle ear disease; had follicular colitis.
- Case 29. P.-m. 441.—With pyæmia from necrosis of the femur; had acute catarrhal colitis.
- Case 30. P.-m. 478.—With uræmic coma and chronic interstitial nephritis; had acute catarrhal colitis.
- Case 31. P.-m. 501.—With cardiac failure from mitral and aortic disease; had hæmorrhagic colitis, with patches of membrane.
1906. Case 32. P.-m. 50.—With chronic interstitial nephritis and lobar pneumonia; had acute colitis with membranous exudation.
- Case 33. P.-m. 260.—With chronic interstitial nephritis and early peritonitis; had acute colitis with membranous exudation.
- Case 34. P.-m. 555.—With erysipelas and acute endocarditis; had acute colitis with membranous exudation.

FIVE CASES IN WHICH ACQUIRED DIVERTICULA OF THE SIGMOID LED TO DEATH.

By

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IN the *Lancet*, March 31st, 1908, p. 843, Dr. Maxwell Telling published a series of sixty-two cases in which death resulted from some pathological complication of acquired diverticula of the sigmoid flexure. Of these cases fifty-three were derived from the scanty and scattered literature of the subject; nine were cases previously unrecorded, and of these three were found in the post-mortem statistics of Guy's Hospital. In his paper Dr. Telling suggests that these conditions are probably much more common than is usually supposed, and urges that in all cases of peritonitis occurring in elderly subjects explored surgically, in the absence of other obvious cause, a special examination should be made of the sigmoid loop of the large intestine. It affords some support to Dr. Telling's contention that in the post-mortem room at Guy's Hospital between January and August of this year no fewer than five cases of pericolicitis, originating in such diverticula, should have occurred.

CASE 1.—Intestinal obstruction caused by a polypus projecting into the sigmoid flexure narrowed by chronic diverticulitis.—E. D., a stout man, æt. 67, was admitted under Mr. Symonds on December 31st, 1909. On December 15th he first had had severe abdominal pain with complete constipation. Purgatives

gave only slight relief, and until admission he had passed only a few small loose stools; flatus had been passed with great difficulty. On admission the abdomen was distended, but not tender. There was movable dulness in the flanks. Palpation revealed no tumour. He was given turpentine enemata without result. On the next day, January 1st, 1910, vomiting began, and Mr. Steward decided to operate. On opening the peritoneum clear fluid escaped, and a mass became palpable in the left iliac region, the exact nature of which could not be determined. It was thought that there was probably a carcinoma of the sigmoid present. A Paul's tube was inserted into the colon above the mass. On January 2nd he was comfortable, but on January 5th his pulse became very rapid and he died.

At the autopsy the colotomy wound was healthy. The sigmoid loop, which was loaded with fat, was bound firmly down to the left iliac fossa by dense adhesions. On opening the bowel a pedunculated polypus was seen attached about six inches above the rectum. The stalk was two inches long and had become twisted, with the result that the polypus, which was about the size of a cherry, was blackened and congested. Its distal end hung down into a narrowed part of the gut, the walls of which were so thickened that for two inches of its length a stout probe could just be passed along the lumen. The mucous membrane was cedematous and congested. Numerous diverticula about one-third of an inch in length and in diameter opened into the stenosed part of the gut. No trace of carcinomatous tissue was found, and there was no ulceration of the mucous membrane. Sir Cooper Perry, who was present, looked upon it as a case of "chronic diverticulitis."

CASE 2.—Chronic intestinal obstruction and general peritonitis from chronic diverticulitis of the sigmoid flexure.—M. A. H., a female, æt. 67, was admitted under Dr. Shaw on January 11th, 1910, for constipation and abdominal pain which had begun gradually six weeks before and had increased in severity. Lately she had sometimes been completely constipated for four or five days, and there had been vomiting on several occasions. Though

still stout, she complained that she had lost weight. On admission the abdomen was tender on palpation in the left iliac fossa. It was generally distended, but mobile and resonant. Masses of faeces could be felt in the colon, and in the iliac fossa a harder mass tender to touch. By rectal examination nothing was felt, but the rectum was ballooned. On January 12th an enema gave a good result, and the patient was better. On January 14th the pain was much more severe, and Mr. Turner decided to operate. On opening the abdomen, general peritonitis was found, and the sigmoid was felt to be densely bound down by adhesions, which were thought possibly to be tuberculous. He closed the abdomen, leaving a drain *in situ*; nothing further was attempted. She died on January 15th.

At the autopsy.—On examining the abdominal viscera *in situ*, the intestines were seen to be a good deal matted together, especially in the left lower quadrant of the abdomen, but in most places they could be separated without difficulty. There was no free fluid, dilatation of vessels, recent fibrin or other evidence of recent acute peritonitis. The small intestine was slightly dilated; the caecum, ascending, transverse and descending colon were much dilated; otherwise they were normal. The iliac colon, and still more the pelvic colon, but not the rectum, were tightly adherent to the neighbouring small intestine; they were surrounded by a thick mass of scar tissue. With much difficulty it was discovered that an enormous number of diverticula with very narrow necks passed from the iliac and pelvic colon in every direction. Many were quite long—an inch or more—and the average diameter was a quarter of an inch. Most of them contained hard faeces. The mucous membrane here was red and in many places ulcerated; some appeared to have ulcerated through to unite with others, but owing to the dense scar tissue surrounding them it was very difficult to make out their relations accurately. The lumen of the colon itself was very narrow, the contraction of the scar tissue having apparently lead to obstruction. There was no evidence of malignant disease. The bladder was not adherent to the colon.

CASE 3.—Acute diverticulitis with general peritonitis.—F. J. K., a stout middle-aged man, æt. 54, was admitted under Mr. Symonds on February 2nd, 1910, for severe abdominal pain and vomiting. It was said that for years he had suffered from attacks of severe abdominal pain with vomiting. On January 27th he had an attack of abdominal pain severe enough to make him call in a doctor. He was given medicine, his bowels were open and he got relief. On February 1st the pain recurred with increased severity. Rectal examination caused great pain. Dr. French, who saw him, diagnosed general peritonitis, and he was removed to hospital. On admission, February 2nd, his pulse was 104 and his temperature subnormal. His tongue was dry and cracked. The abdomen was distended and rigid. There was movable dulness in the flanks. Pain and tenderness were not more marked in the left iliac fossa than elsewhere. Mr. Hughes operated immediately. On opening the abdomen turbid fluid escaped in quantity. His condition only allowed time for a drainage-tube to be inserted, and he was put back to bed.

At the autopsy there was diffuse general peritonitis with a great effusion of turbid serum. The appendix, though coated with pus, was not gangrenous or especially inflamed. The left iliac fossa was occupied by a hard mass covered with a thick coating of lymph. On handling this and separating the thick lymph, a small faecal concretion escaped from a perforation in the gut. On opening the gut it was seen that a diverticulum of the walls, formed by a hernia of the mucous membrane into an appendix epiploica, had ruptured at its apex and discharged the concretion. The walls of the diverticulum were acutely inflamed, dark and gangrenous. To exclude the presence of carcinoma a vertical incision was made through the mucous membrane. This appeared normal. Several other diverticula were found in the gut in series, but no others contained a concretion or showed any signs of inflammation. There was no evidence of any chronic inflammation and no stenosis of the bowel. The whole process was very acute, comparable to that of an acute perforating appendicitis.

CASE 4.—Chronic pericolitis with general peritonitis.—E. A., a male, æt. 48, was admitted on April 15th, 1910, with a history of abdominal pain for three months. The pain was referred to the left side of the abdomen. At times there had been diarrhœa, but no blood or mucus. Vomiting had been very frequent. For the last three days his bowels had not been open. On admission he was found to be wasted and thin, the abdomen was tense and distended, not very rigid, and mobile. There was a large very hard mass in the left iliac region, over which a dull note was obtained on percussion, but which was not in the least tender. On the following day Mr. Turner operated. A large mass was felt in the left iliac fossa through which the sigmoid flexure ran. A lateral anastomosis between the ileum and the colon below the tumour was performed. The abdominal wound became infected and, after becoming gradually weaker, the patient died on April 28th.

At the autopsy the laparotomy wound was sloughing and unhealthy. There was recent general peritonitis without much exudation except in the left iliac fossa, where some pus escaped from among some matted coils of intestine. This abscess was recent, but fairly well demarcated. At this point several coils of small intestine were adherent by old fibrous tissue to the sigmoid flexure of the colon, which was firmly bound down by old inflammation. No growth was discovered, and it was considered that the mass in the left iliac fossa, which was so adherent and firm, was due to inflammatory change and local peritonitis such as might have occurred around a sacculus of the large intestine. There was no actual stenosis of the bowel, and death was due, not to strangulation, but to peritonitis, the extension probably from older local inflammation in the left iliac fossa.

CASE 5.—Acute diverticulitis due to the impaction of a fish bone in an acquired diverticulum of the sigmoid with general peritonitis.—D. N., æt. 73, a stout woman, was admitted on August 4th under Sir Alfred Fripp for abdominal pain of great severity, constipation and vomiting, beginning on August 1st. The temperature was subnormal, the pulse 120. A femoral

hernia, which was irreducible, was present on the right side. The tongue was dry and furred. The abdomen was distended and tense. On rectal examination a bulging was felt in Douglas' pouch. Under local anæsthesia an incision was made over the femoral hernia. The sac was found to contain pus. The abdomen was drained, and the patient put back to bed as quickly as possible in a moribund condition. She died a few hours later.

At the autopsy there was general peritonitis, and the pelvis was full of pus. The stomach, gall-bladder and vermiform appendix were found healthy. On turning to the sigmoid it was found that at the lower end of the loop the gut was adherent to the posterior pelvic wall at two points. On separating these a recent abscess cavity was opened. The gut was soft and friable. On cutting it open a yellow bile-stained fish bone, an inch in length, was found projecting into the lumen of the gut. About half its length was free, the rest lay in a diverticulum about half an inch in length, the apex of which was perforated and covered with thick yellow lymph. A probe was passed into at least three other diverticula opening at a higher level. There was no ulceration of the mucous membrane, which was thick and cedematous, and made the finding of the orifices of the diverticula a slow and difficult task. Had the fish bone not protruded and pricked the examining finger, examination might have failed to discover the diverticulum.

REPORT OF THE ARTHUR DURHAM TRAVELLING STUDENT.

By

W. M. MOLLISON.

I WAS absent from England from the beginning of October, 1909, to the beginning of April, 1910. Of these six months, three (October, November and December) were spent in Vienna; two (January and February) in Berlin; and the remaining one in Freiburg-in-Baden. Between Berlin and Freiburg I visited Homburg and Wiesbaden.

At each of the centres I studied ear, throat, and nose work, and visited the surgical kliniks.

VIENNA.

For *Aural Work* I attended Professor Alexander's Klinik. The professor held a series of lectures on the Surgical Aspect of Ear Disease. In this course he discussed the pathology, diagnosis and treatment of ear disease, demonstrating patients in support of his statements.

During the three months I worked under one of the assistants in the Out-Patient Department, and was thus enabled to obtain practical experience in the systematic examination of patients, to apply various forms of treatment, and to estimate to some extent the results obtained from out-patient treatment and operations.

This klinik may be taken as the type of all kliniks on the Continent. It consists of an In-Patient and an Out-Patient Department, the whole under the care of a professor. Under the professor are four assistants, who are qualified men, and who devote themselves to the work of the klinik. The Out-Patient Department is open daily, and the assistants treat out-patients. When a case of special interest is seen, it is handed over to the "first assistant," probably a man of six or seven years' experience, who in his turn can, if he wishes, hand it on to the professor; such cases and those requiring operation are taken as in-patients. The professor gives courses of demonstrations for students once a week during the winter and summer sessions, showing cases selected for him by the assistants. He also gives post-graduate courses almost all the year round. Post-graduates are also allowed to work in the Out-Patient Department either under the charge of one or other of the assistants, or as voluntary assistants.

As aids to the various lectures and demonstrations there are an excellent collection of anatomical specimens and models, a large number of pathological specimens, and many microscopical sections. There is a well-equipped laboratory in connection with the klinik.

As a result of this system every out-patient gets the individual attention of a specialist, and has treatment applied, if necessary, every day; further, time is found to make elaborate investigations in those cases that require it without dislocation of the conduct of the Out-Patient Department. Since, too, the assistants are more or less experts, they are in a position to carry out special lines of investigation for themselves, or to work out some point suggested by the professor.

Lastly, voluntary assistants are accepted for work in the klinik; such men serve perhaps six months or a year, and see all the work of the klinik and get considerable practical experience therefrom.

For Throat and Nose Work I attended Professor Chiari's Klinik and Out-Patient Department, taking a course with one

of the assistants (Dr. Marschik); I also took courses with Dr. Glas and Dr. Koschier, and attended the latter's Out-Patient Department throughout the three months; in addition, I attended some demonstrations by Dr. Hajek.

These courses, generally of four weeks' duration, consisted partly in the practical examination of patients, and partly in demonstrations of selected patients and discussion of the pathology, diagnosis and treatment of the conditions exhibited by them. In his course, Dr. Koschier gave some ten lectures illustrated by anatomical specimens, and for the rest patients were examined under the tutelage of the assistants, and the simpler forms of treatment carried out. Those attending the kliniks have opportunities of seeing in-patient operations; I thus saw many of the major nose and throat operations, *e.g.*, partial and complete laryngectomy, radical operations on the frontal and maxillary sinuses.

Perhaps the most striking point about the throat and nose work in Vienna is the very great number and variety of cases. All Out-Patient Departments are open every day, and all always crowded. The methods of examination differ only in slight degree from those used in the Guy's Throat Department. The methods of treatment present some points of difference, more local applications are used, intranasal powders and applications and intralaryngeal insufflations, and more out-patient operations under cocaine are carried out.

Direct laryngoscopic, tracheal, bronchoscopic and œsophageal examinations are made in the Out-Patient Department *under cocaine*, with Brüning's instrument; the results, however, are not always satisfactory.

To study *General Surgery* I attended the large General Hospital and the Wiedner and Rothschild Hospitals. In the General Hospital I watched operations in the kliniks of Professors Eiselsberg and Hochenegg, and visited the klinik of Professor Lorenz.

The operative methods in use differ little from those at Guy's. The precautions taken to ensure asepsis vary in the different

kliniks; in that of Professor Eiselsberg, overalls, gloves, caps and masks were worn (the rubber gloves, as in all the kliniks I saw, being sterilised dry), and the operator and assistants wore white cotton gloves over the rubber ones, and changed them when necessary in the course of the operation. These cotton gloves seemed most useful in abdominal work. In Professor Hochenegg's klinik gloves were worn, but not caps or masks, and in another klinik, neither gloves nor caps.

The orthopædic work in Professor Lorenz's klinik was very interesting, but the interest mainly lay in technical details. An apparatus for supporting patients while plaster splints were applied, was in all ways admirable.

At the Wiedner Hospital (about 600 beds), Professor Schnitzler is in charge of the Surgical klinik, and has 150 beds under his care. This is not a teaching hospital, and in consequence no students work there. The professor, however, not only kindly invited me to attend his operations, of which I saw a large number, but also put me under the guidance of his first assistant, whom I accompanied in his visits to the wards. The condition of the wards in this hospital and in the general hospital (both old buildings) is strikingly different from that in a London hospital. They are bare and unattractive in appearance, and overcrowded; the beds are placed at a distance of about eighteen inches; there is no effort made to screen off patients; and the numbers of the nursing staff (nursing sisters) are inadequate as judged by our standard.

I saw the Rothschild Hospital a few times only. This is comparatively new, the wards are bright and not over-filled, and the nurses are "trained."

In all kliniks the operating theatres are large, have tiled (or concrete) floors and walls, and have either a north light or arc lamps, and an arrangement of mirrors to throw the light on to the operation area. The sterilising arrangements for instruments are good, and dressings, towels, etc., are sterilised in tins.

BERLIN.

Aural and Nasal Work.—I became a voluntary assistant in the “private” klinik under the charge of Drs. Jansen and Kobrak for a month, and during both January and February attended the operations of Dr. Jansen, seeing here many ear and nose operations.

I took a course on the pathology of the ear under Dr. Wagener, the chief assistant to Professor Passow in the Charité Hospital. Here, too, I saw the conduct of the Out-Patient Department, and was enabled to see operations in the klinik. I also visited the fine new Rudolf Virchow Hospital just outside Berlin, and saw Professor Hartmann, who has charge of the ear, throat, and nose klinik. This is the largest hospital in the world; it contains between 2,000 and 3,000 beds, and on emergency is capable of holding 500 more. All the departments have separate buildings, the buildings themselves being only of two stories. The wards are very bright, and are tiled with hexagonal cream-coloured tiles on floor and walls.

The work in Dr. Kobrak’s Out-Patient Department was entirely practical, and consisted in examining patients and treating them. In this klinik the examination of the patients before operation is very simple in comparison with that used in Vienna, or in the Charité Hospital. In the Charité Hospital the views on ear testing differ a good deal from those in Vienna. The methods used are all in the direction of greater accuracy in testing the cochlea, while less importance is attached to the functional examination of the semicircular canals.

Throat and Nose Work I studied under Professor Edmund Meyer, acting as voluntary assistant in his private klinik for one month; in this capacity I examined the patients and applied treatment. The methods of examination and treatment in vogue here differed only in minor practical points from those in Vienna.

For General Surgery I attended Professor Bier’s klinik. In a theatre accommodating about 130 students, the professor

lectures at 8 a.m. five days a week and demonstrates on selected cases, on which he subsequently operates. The teaching is essentially for the students, and resembles a combination of clinical lecture and out-patient teaching as practised at Guy's, the difference being that the cases are in-patients, and that they have all been thoroughly investigated in the wards before demonstration.

The theatre appointments are excellent, all being arranged with a view to asepsis—towels and dressings sterilised in tins with lids which can be opened by a handle worked from a foot piece. The surgeon and assistants wear gloves, but no caps or masks.

The cases for operation succeed one another very quickly, no time being allowed to elapse between any two operations. This is due mainly to the system of assistants, of whom Professor Bier has a great number. Some complete the sewing up of the wound of one patient, some assist the professor at another operation, while yet others prepare a third patient for operation. But a further factor of great influence is the use of local, spinal or venous anæsthesia, for, once the patients have received their injections of anæsthetic, they can wait already prepared for operation at any moment, so that several operations can be carried through in a very short time.

I saw also the Out-Patient Department in connection with this klinik. It comprises in itself many departments:—casualty cases are treated; congestive treatment (Bier's treatment) applied to all parts of the body; minor operations performed; massage carried out; hot-air treatment for stiff joints applied; orthopædic apparatus made for patients; and one room is devoted entirely to the teaching and carrying out of special exercises for the cure of cases of spinal deformities. Each of these departments is under the care of one of the assistants, who is himself a specialist in that department, and each of these "specialists" has qualified workers under him.

FREIBURG.

I visited Freiburg in March. For *Aural Work* I attended the klinik of Professor Bloch, and saw the methods employed by the professor and his assistants in the diagnosis and treatment of out-patients; in this klinik both ear and nose patients are seen

For *Throat Work* I attended Professor Killian's klinik, and saw many cases of interest. Here, as in Berlin and in Vienna, X-ray photographs to show the condition of the sinuses in connection with the nose are always used, both as an aid to diagnosis and as a guide to operation.

The aural work in Professor Bloch's klinik is far less in amount than in the Berlin or Vienna kliniks, but it presented a most interesting feature. The cochlea testing was conducted on more scientifically accurate lines than in either of the other centres; it follows the Munich rather than the Viennese school.

General Surgery.—I saw in the klinik of Professor Kraske many interesting operations. The cases were mainly gall-bladder and thyroid. I saw also some abdominal surgery in Professor Krönig's klinik (gynæcological); here the strictest asepsis is practised. Lastly, I met Professor Goldmann, who showed me over his hospital and demonstrated some most interesting cases. I was unfortunate in seeing him operate only once.

REMARKS.

(A) AURAL WORK.

In the *Guy's Hospital Gazette* (March, 1910) I gave a full account of the methods in use in the Alexander Klinik for the functional examination of the cochlea and semicircular canals; here a short account will be given that the methods in vogue in Vienna may be compared with those in Berlin and Freiburg.

When a patient with otitis media is to be fully examined, whether for purposes of diagnosis or previous to operation, tests are applied for the study of the cochlear condition and for the study of the semicircular canals, quite as much attention being devoted to the latter as to the former. That this should be so in Vienna is most natural, as it was here that "caloric" and "galvanic" nystagmus were first discovered and studied.

In Professor Alexander's Klinik the following table is used to systematise examination:—

R.	Conversation speech.	L.
	Whispered speech.	
	Acumeter.	
	Weber.	
	Schwabach.	
	Rinné.	
	C ¹	
	A	
	C ₄	
	Galton's Whistle.	

Spontaneous nystagmus.
 Caloric nystagmus.
 Rotation nystagmus.
 Galvanic nystagmus.
 Disturbance of equilibrium.
 Speaking tube.
 Fistula symptom.

It will be noticed that almost as many tests are applied to the vestibular apparatus as to the cochlea. Should the patient exhibit spontaneous nystagmus, he is tested by three separate methods—by being turned on a revolving stool ("rotation"), by having cold water syringed into the ears, and by having galvanism applied to the ear. All these tests produce vertigo (therefore nystagmus) of greater or less severity, and the results given show whether the labyrinth is still excitable or whether

one labyrinth is more excitable, and may give indications for opening the semicircular canals and vestibule.

The fistula symptom requires a word of explanation. Should there be, as a result of middle ear suppuration, a defect in the bony outer wall of the external semicircular canal, pressure on this canal will produce vertigo. In a suspected case pressure can be applied to the canal by raising the pressure in the external auditory meatus. This is done by means of a Politzer's bag and a suitable earpiece. Should a fistula exist, the patient will feel giddy on compression or on decompression of the air in the meatus, and the resulting nystagmus can be observed. Unfortunately there are fallacies and even dangers in this test.

It may be noted that to test the cochlea the Weber, Schwabach and Rinné's tests are employed, all by means of the A fork; beyond these only two forks, the low C_1 (of 60 vibrations) and the high C^4 (of 2048 vibrations), and Galton's whistle are used.

In Berlin and Freiburg, for the examination of cases of otitis media, far more attention was paid to cochlea testing than to vestibule testing.

In the University Klinik in Berlin not only were the Weber, Schwabach and Rinné tests employed, but the *lower tone limit* and the *upper tone limit* of each patient was determined. The lower tone limit normally is a note of 16 vibrations per second, and the upper tone limit one of about 28,000 vibrations per second. To determine the lower tone limit special forks are required; those made by Professor Edelmann, in Munich, are universally used. To determine the upper tone limit two means are employed, one, the Galton whistle—the principle of which is a short organ pipe, and the other, the Monochord, a horizontally stretched wire which can be altered in length, and which is made to vibrate in its length by the rubbing along it of a piece of lint covered with resin. [It should be said that the complete series of forks is used also in Vienna whenever fuller information on the cochlea is required, as, for example, in deafmutism, in syphilitic deafness, and so on.]

The vestibule is only investigated when there seem to be indications for doing so; the presence of spontaneous nystagmus is always noted, and should there be a question as to whether a patient, with otitis media, has trouble extending into the inner ear, the "caloric" test is applied, but the "rotation" and "galvanic" only very occasionally. The workers on the subject state that quite as much information can be obtained from careful testing of the cochlea—especially the upper tone limit—as from the various nystagmus tests; in support of their statements it is pointed out that the cochlea is an extremely delicate mechanism, and any change in the direction of the inflammation in the vestibules or canals will affect the cochlea at once. Further, it is quite rare for cases to occur in this klinik which require an operation on the labyrinth.

In Freiburg, in Professor Bloch's klinik, the testing of the cochlea is also very fully carried out; that of the vestibule takes a secondary place. Here, as in Berlin, it is thought that the full examination of the condition of the semicircular canals is seldom needed, and that cases requiring operation on the labyrinth rarely occur.

For all cases of deafness of doubtful origin great accuracy is aimed at in examination. In testing for hearing to speech, different words are used in which the sounds produced are high or low; thus, such words as "six," "fifteen," "people," have a comparatively high sound, while "murmur," "purple," "organ," have a low sound. By using these words it is possible to get a rough idea as to what form of deafness is being dealt with; when the conducting apparatus is defective the "high" words are heard better than the "low" ones, and when there is nerve deafness, the "low" better than the "high."

For testing the duration of bone conduction an "A" fork is used, with a Kittlitz attachment. This arrangement shows the examiner when the fork has reached a definite intensity of vibration, and he can then place the fork on the patient's head, and notice by means of a stop watch exactly how long it

is heard. This method is more scientific than that by which the examiner compares the patient's perception with his own, since it eliminates the personal factor.

Rinné's test is performed carefully, not only with the "a'" fork, but in cases of doubt with a fork an octave below, and even with a third fork intermediate between these. In this klinik it was maintained that by these accurate observations the diagnosis of otosclerosis, even in early cases, is made fairly certain. For the diagnosis of this disease, too, Gellé's test was much used, and was held quite reliable, a view contrary to that held in Berlin and Vienna.

The operative work in all the centres was good, but presented no very striking or new aspects; the operation performed for chronic suppurative otitis media is almost invariably the radical mastoid operation; ossiculectomy is rarely used, as experience there has shown that it does not effect a cure of the disease.

CONCLUSIONS.

1. In Vienna great attention is paid to the labyrinth and its functional testing in cases of chronic suppurative otitis media.

2. In Berlin and Freiburg much attention is paid to the functional examination of the cochlea, and less importance attached to the labyrinth testing.

3. In Freiburg greater accuracy of examination of patients in some directions is found than in the other centres.

4. Operative work is good; in the case of chronic suppurative otitis the radical mastoid operation is performed in preference to intermeatal operations.

(B) SURGERY.

From an operative point of view the general surgery does not, in my opinion, reach the standard set at Guy's. The best work was, I think, in Vienna. From the point of view of outfit, all centres I visited are much in advance; the theatres are larger and more convenient, the sterilising apparatus for instruments is more excellent, and all dressings are sterilised in tins

and are never touched by any but the assistants. By "dressings" is meant sponges, gauze, pads, wool, and bandages. As to the operators' own precautions, some surgeons wear gloves, cap, mask, and overall with long sleeves, others wear only an overall with short sleeves. The preparation of the patient is in all kliniks simple. Except in Professor Eiselsberg's klinik, "compresses" are not used; sometimes the patient is prepared entirely on the table, more usually the skin is shaved beforehand, and immediately before operation some antiseptic is rubbed over, either tincture of iodine or formalin in spirit, or benzin and ether.

(C) ANAESTHETICS.

There are no specialist anaesthetists in Austria or Germany attached to the kliniks as far as I could discover: all the assistants give anaesthetics. The apparatus used is either a simple form of mask with three or four layers of gauze, or the Roth-Dräger apparatus for giving oxygen with ether or chloroform (or both). I never saw a Glover's inhaler, a Rendle's mask, or an Ormsby inhaler, nor a nitrous oxide apparatus. Ether and chloroform are used and some ethyl chloride, for which there is a special inhaler. Ether is used much more than chloroform. For all operations the patient is strapped to the table. In some of the kliniks insufficient attention was, in my opinion, paid to the anaesthetic, the administrator not appearing to appreciate the depth of anaesthesia, though, as a rule, too light an anaesthesia was maintained.

In Berlin, in Professor Bier's klinik, the anaesthetics are a special feature. More patients are operated on under local, spinal or venous anaesthesia than under ether or chloroform. For the guidance of administrators of general anaesthetics there is a list of rules posted in Bier's operating theatre. The most important are here given *in extenso*:—

1. The assistant who undertakes giving an anaesthetic must go on with that anaesthetic, and has entire responsibility: he can only hand it over to another if the responsibility is definitely handed over too.

2. The administrator must know about the condition of the patient's heart, lungs, teeth, and urine.

3. He must know whether any injections have been given beforehand.

4. All patients, before ether anæsthesia, are given an injection of a mixture of morphia 0.01, atropine 0.001.

Adults	0.01	grm.
Weak Patients	0.005	„
Children	0.0025	„

5. The anæsthetist is given an ether drop-bottle, mask, tongue forceps and gag.

6. If the surgeon demands it, the anæsthetist must give chloroform.

7. If required, he must give an aseptic anæsthesia.

8. This paragraph gives the reasons for troubles met with during an anæsthetic.

And No. 9 explains what to do should trouble arise from failure of respiration or heart.

Perhaps the fourth rule is the most striking; all patients are given morphia and atropine before ether. Certainly with this there is less trouble in inducing anæsthesia, naturally less anæsthetic is required, and shock is diminished.

For *local anæsthesia* novocain one-half per cent. solution is used, plus a small amount of adrenalin; of this solution large amounts are injected (I could not exactly discover the limit, but I saw 90 c.c. injected in one case—umbilical hernia). A syringe with a special long flexible needle is used for making the injections. By means of this local anæsthesia almost every part of the body can be operated on; *e.g.*, I saw excision of superior maxilla quite painlessly performed under it.

For *venous anæsthesia* novocain one-half per cent., without adrenalin, is used. The principle of this method of anæsthesia is to make the part in question absolutely bloodless and to shut it off from the circulation with a rubber bandage: a vein of

the part is exposed and the novocain injected into this vein which distributes the anæsthesia all through the part. Anæsthesia is complete in quite a few minutes, and after the operation the novocain can be syringed out by means of salt solution.

The custom of giving a preliminary injection is the rule in Dr. Jansen's klinik, and his patients are also given ether in a special little canvas inhaler very easy to sterilise.

In Freiburg the custom is to give scopolamine and morphine to every patient before operation. Here, too, there is in use an apparatus for giving oxygen and anæsthetic under pressure to patients where intrathoracic operations are being performed.

Two points stand out with regard to general anæsthetics; first, an almost invariable use of a preliminary injection either of morphine and atropine or scopolamine and morphine; and second, the excellence of the Roth-Dräger apparatus for continuous oxygen and ether or chloroform. But the administration of anæsthetics, on the whole, is not so good as that seen in Guy's, and the patients are treated with less consideration.

THE SENSIBILITY OF THE ALIMENTARY CANAL.*

By

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THE histological investigations of Gaskell, Langley and others have proved that all the viscera are supplied with afferent as well as efferent sympathetic nerves. Experiments on animals and observations on human beings have shown that the impulses conveyed by these afferent nerves give rise in peripheral or central nerve-centres to important reflexes, the activity of all the organs of the body being controlled to a great extent by reflexes of this sort. Under normal conditions the afferent nerves of most organs convey impulses without sensation of any kind being experienced.

The swallowing of food at the body temperature produces no sensation after the pharynx has been passed, and no indication of its passage through the stomach and intestines is felt until fæces enter the rectum immediately before defæcation. The experience of every-day life has, however, led to the belief that the alimentary canal, though not endowed with the sensa-

* A preliminary account of this investigation was published in the *Journal of Physiology*, vol. xxxvii., p. 481, 1908.

tion of touch, can yet be the seat of painful and thermal sensations. A feeling of cold or heat in the epigastrium is experienced after swallowing cold or hot food, and a burning sensation can often be recognised in the same situation after drinking strong alcoholic fluids. Under numerous abnormal conditions pain, which feels as if it were situated in the stomach and intestines themselves, is experienced.

In the last few years the observations of Lennander and James Mackenzie have thrown doubt upon these wide-spread beliefs, and many people have now accepted their teaching that the viscera, being supplied only by the autonomic (sympathetic) nervous system, are completely insensitive, and that the true seat of abdominal pain is in one or other of the structures of the abdominal wall, which receive their sensory nerve supply from the ordinary cerebro-spinal nerves.

The new doctrine appeared to us to be so revolutionary, and the data upon which it was founded so incomplete, that we have attempted to obtain more definite information as to the sensibility of the healthy stomach and intestines to various forms of stimulation. The subject of gastro-intestinal pain will be discussed in a later paper.

I.—TOUCH, HEAT AND COLD.

A number of observations have already been made on the subject of temperature sensation in the stomach and intestines, but the results obtained are contradictory.

In 1889 Quincke* passed cold and hot water into the stomach of a boy through a gastric fistula. With cold water he had a local feeling of cold accompanied by shivering, and warm water produced a vague uncomfortable sensation. In 1905 Head, Rivers and Sherren† investigated the sensibility of the colon in patients, who were not cachectic and on whom colotomy had been performed. A tube was passed through a ring of mucous membrane into the lower portion of the colon, which practically formed an isolated loop of gut. It was found that "water at 40°C. and at 20°C., which seemed warm and cold respectively to the skin of the abdomen, were entirely unappreciated when applied within the walls of the gut. But ice water was at once called 'cold,' water at 50° was said to

* H. Quincke. *Wien. klin. Woch.*, xix., 923, 1906.

† H. Head, W. H. Rivers, J. Sherren. *Brain*, xxviii., 99, 1905.

be uncomfortable, and two patients of unusual intelligence spoke of the stimulus as 'hot.' This sensation of heat or cold was never localised in the abdominal cavity. If the patient was asked to indicate the position of the stimulus, he either placed his hand over the region of the navel or pointed into the air."

Neumann† in 1905 found that patients immediately felt a sensation of heat and cold when hot and cold water were respectively poured through a double tube into the stomach. After a short time the sensation produced by water at 25°C. disappeared, after which water at 10°C. no longer produced any sensation at all. Neumann states, moreover, that in hysteria there is sometimes anæsthesia to temperature, and at other times cold is felt as hot or burning, and water at 25°C. is felt as very cold. J. Ch. Roux** found by introducing water into the stomach by means of a tube that hot and cold were felt, and that a difference of temperature of a few degrees between hot fluids introduced successively could often be recognised. On one occasion only did he find that a patient had no sensation of temperature in his stomach, but he could offer no explanation for this exception. On the other hand, L. R. Müller†† found that no patients experienced any sensation of cold when the stomach was washed out with ice water; but on touching the rectal mucous membrane with a hot glass rod during an examination with a proctoscope he found that the patient experienced a sensation of discomfort and warmth, localised near the symphysis pubis. He also states that cold can sometimes be felt by the rectum. Finally, Becher‡‡ found, as a result of observations which were published at the same time as our first communication on the subject, that the stomach is insensitive to heat and cold. The œsophagus, however, was sensitive to these stimuli, except in his own case, as he experienced no sensation of any sort after hot or cold water had passed his pharynx.

The contact of chemically inert substances at the body temperature with the mucous membrane of the œsophagus, stomach and intestines, gives rise to no sensation of any sort. This was proved by introducing such substances through a tube into the stomach and intestines by the natural passages in normal individuals, and by the artificial openings in patients on whom a gastrostomy or colotomy had been performed. In the case of the œsophagus the absence of tactile sensibility was proved by pouring thick fluids down an indiarubber tube, the lower end of which was situated at various points in the œsophagus.

† A. Neumann. *Wien. klin. Woch.*, xix., 923, 1906.

** "Maladies du Tube Digestif," edited by Debove, Achard and Castaigne, i., 375, Paris, 1907.

†† L. R. Müller. *Mitteil. aus den Grenzgeb. d. Med. u. Chir.*, xviii., 600, 1908.

‡‡ E. Becher. *Zeits. f. Psychologie*, xlix., 341, 1908.

The complete absence of any sensation under these conditions suggests that the uncomfortable sensation experienced on swallowing a hard or large object, and the sensation of obstruction in the œsophagus experienced by patients with œsophageal stenosis, are due to distension and originate in the muscular coat and not in the mucous membrane. Confirmatory evidence of this will be published in a later paper.

With regard to thermal sensations, our results in the case of the stomach are in opposition to those of Quinke, Neumann and Roux, and agree with those of Becher and Müller so far as the latter go. We found that, on introducing ice-cold water or hot water at any temperature between 40° and 50°C. into a normal stomach, no sensation of any sort was produced. We have little doubt that Roux's results were due to his having employed an ordinary stomach tube. When hot or cold water is passed through such a tube, its outer surface rapidly becomes hot or cold, so that the thermal stimulus can act upon the œsophagus. We have used a double tube, an india-rubber tube of 5 mm. diameter being introduced into an ordinary stomach tube. With this arrangement three or four ounces of water can be passed down the inner tube before the outer surface of the stomach tube becomes definitely hot or cold. Accordingly we have found, after passing the double tube into the stomach, that a sensation of heat is only produced when more than three or four ounces of hot water are poured down, an ill-defined sensation of heat being then experienced in the epigastrium, which is no doubt due to conduction of the heat to the œsophageal wall. As much as half a pint of ice-cold water can, however, be introduced without the sensation of cold being felt. In neither case is any other sensation experienced, the individual being completely unaware that anything is passing into his stomach.

These observations made it probable that the sensation felt when hot and cold fluids are swallowed is produced in the œsophagus. This was proved to be the case by introducing the tube a distance less than 40 centimetres from the teeth, so that its end was in the œsophagus, a short distance above the cardiac

orifice of the stomach. On now pouring down water at 0° and at 40° or 50° a sensation respectively of cold and heat was produced after a latent period of between half and one second, its character and indefinite localisation deep in the epigastrium being exactly the same as when the fluid is swallowed in the ordinary way. On now pushing the tube into the stomach and pouring hot and cold fluid down, no sensation was produced. We have repeated the experiment in four individuals in a still more conclusive manner. Hot and cold water were poured into the stomach; no sensation was experienced. On now pulling the tube up so that its lower end did not quite reach the cardia the temperature sensation was felt. X-ray observations showed that the localisation of temperature sensation in the œsophagus is very accurate, the individual putting his finger on a point in his epigastrium, which is generally within an inch of the region occupied by the lower end of the œsophagus, as projected on the anterior surface of the body.

Some observations made on a young woman who had had a gastrostomy performed for a fibrous stricture of the œsophagus, which followed the swallowing of strong hydrochloric acid, and on three men who had undergone the same operation for epithelioma of the œsophagus, confirmed our belief that the gastric mucous membrane is completely insensitive to thermal stimuli. Hot and ice-cold fluids were poured through a catheter, which was passed through the gastrostomy tube, this double-walled channel being used so as to prevent the skin surrounding the opening from being warmed or cooled. It was found that no sensation of temperature or of any other description was experienced.

On paying accurate attention to the sensation produced after drinking a mouthful of very hot or cold fluid, it was now recognised that the sensation in the epigastrium began about three seconds after the swallowing act, and lasted for about three seconds. On simultaneously listening to the epigastrium it was found that the second deglutition sound, which begins

immediately after the last trace of food has entered the stomach,* began immediately after the sensation disappeared. Hence the period during which the sensation is felt must be that in which the fluid is collected in the lower end of the œsophagus and is slowly passing into the stomach. The observations, described in our paper published in the Guy's Hospital Reports for 1907 on the process of swallowing, combined with these experiments on temperature sensation, show that the feeling of heat and cold, experienced when hot and cold fluids are drunk, and until now almost universally ascribed to the stomach, really originates in the lower end of the œsophagus, and corresponds in duration with the period in which the fluid is passing through the cardiac orifice into the stomach.

James Mackenzie† ascribes the sensation of heat and cold in the epigastrium after drinking hot and cold fluids to reflex vascular changes in the skin of that area, and he believes that the skin is actually the seat of the sensation. We have disproved this theory by placing ice over the skin of the epigastrium so that a maximal sensation of cold was produced; ice-cold water was then poured into the œsophagus through a tube, and immediately a sensation of cold was felt in a situation deeper than that simultaneously present as a result of the contact of the ice with the skin. On another occasion the skin of the epigastrium was warmed by a flask containing water at 48° C., and water at the same temperature was poured through a tube into the lower end of the œsophagus. A sensation of heat deeper than that felt in the skin was produced. Suggestion was excluded by blind-folding the individual and pouring hot and then cold water down without saying which was to be done first; the temperature was recognised immediately in both cases.

Our observations on the sensibility of the colon to temperature are not in complete agreement with those of Head and Müller. By introducing hot or cold water through a double tube into

* Vide our observations on this subject in the Guy's Hospital Reports, lxi., 401, 1907.

† James Mackenzie. *Symptoms and their Interpretation*, p. 125, London, 1909.

the colon we found that the mucous membrane of the large intestine is as insensitive to temperature as is that of the stomach. A double tube is required, as otherwise heat or cold is felt in the sensitive anal canal, and it is then difficult to be sure whether the sensation is present elsewhere as well. We have used for the purpose an ordinary rectal tube, through which has been passed a small india-rubber tube just large enough to fit tightly in the round opening at the end of the former. We obtained the same result in six patients, on whom colostomy had been performed for stricture of the rectum, by introducing hot and cold fluids through a tube directly into the colon. The exposed mucous membrane was moreover completely insensitive to hot and cold, as well as to touch.

It has often been suggested that discomfort and pain in the stomach, in the absence of organic disease, may be due to hyperæsthesia of the mucous membrane, which becomes capable of producing sensations in response to stimuli, which are normally without effect. We have had the opportunity of testing this theory in a case in which it seemed possible that the symptoms might be due to hyperæsthesia of the gastric and intestinal mucous membrane to thermal stimuli. A man, 52 years old, complained of a burning sensation inside his abdomen which had been present for thirty years, but had recently become almost unbearable. The sensation was constantly present and was worse in hot weather. Hot food produced an immediate aggravation, and the patient was convinced that he could feel it enter his stomach, which was the chief but not the only seat of the burning sensation. For years he had taken very little hot food, and had been in the habit of drinking iced water at all hours of the day. This always produced a temporary diminution in the sensation of heat, and he obtained a similar result by injecting ice-cold water into his colon. After blind-folding the patient, we poured very hot and very cold water into his stomach and colon through a double tube; he did not feel the slightest thermal or other sensation. The feeling of heat was therefore entirely mental in origin, and the relief given by cold drinks and cold enemata was the result of suggestion.

II.—EFFECT OF HYDROCHLORIC ACID.

The few observations which have been published on the sensibility of the gastric mucous membrane to hydrochloric acid are so contradictory that no reliable conclusions can be drawn from them.

Talma* in 1884 found that normal individuals experienced no pain when dilute hydrochloric acid was poured through a tube into the stomach, but that pain was felt in cases of nervous dyspepsia. In 1892 Löwenthal† poured 250 c.c. of hydrochloric acid of various concentrations at the body temperature through a tube into the stomach, in which it was left for one minute. In four normal individuals no sensation was produced by a 0·3 per cent. solution; in three of the four a warm sensation was felt with a 0·4 per cent. solution, and in the only individual on whom he tried a 0·5 per cent. and a 0·6 per cent. solution a feeling of warmth was also produced. In two cases of "atonic stomach" and in one of dilation warmth was felt, but no sensation was produced in cases of gastritis and ulcer. In no case was the sensation painful. Bönninger‡ in 1908 found, however, that although 100 c.c. of a decinormal solution of hydrochloric acid produced no sensation in the normal stomach after washing out with 100 c.c. of water, a violent pain, which could be temporarily relieved by milk, was always produced in cases of gastric ulcer. Heineke and van Selms** made no observations with hydrochloric acid in normal individuals, but they found that in two patients with gastric ulcer, and in two suffering from symptoms suggestive of the same disease, a sensation of pain was produced on introducing hydrochloric acid, varying in strength from 0·1 to 0·4 per cent., through a tube into the stomach.

Our own observations show that 0·4 and 0·5 per cent. hydrochloric acid, introduced into the empty stomach of normal individuals through a tube, produces no sensation of any kind. If the tube does not reach as far as the cardiac orifice, so that the acid enters the lower end of the œsophagus, no more sensation is produced, unless the fluid is cold, in which case the ordinary œsophageal sensation of cold is produced. The introduction of 0·5 per cent. hydrochloric acid through the gastrostomy wound into the stomach of patients with œsophageal stenosis also produced no sensation.

* S. Talma. *Zeits. f. klin. Med.*, vii., 407, 1884.

† M. Löwenthal. *Berl. klin. Woch.*, xxix., 1188, 1892.

‡ M. Bönninger. *Berl. klin. Woch.*, xlv., 396, 1908.

** D. Heineke and M. van Selms. *Arch. des Mal. de l'Appar. dig.*, ii., 467, 1908.

Since the preliminary account of our observations were published they have been confirmed by J. E. Schmidt,† who found that the introduction of from 15 to 30 c.c. of 0.5 to 2.0 per cent. hydrochloric acid through a gastrostomy wound into the empty stomach of three patients, and through a stomach tube into his own stomach, produced no sensation.

It is thus clear that the pain, which is often associated with the presence of excess of free hydrochloric acid in the stomach, cannot be due, as has generally been believed, to the excess of hydrochloric acid alone, as it is very improbable that as much as 0.5 per cent. free hydrochloric acid is ever present in the stomach. Moreover, many cases of "hyperchlorhydria," discovered by chemical analysis, are not associated with pain or other gastric symptoms, and the hyperchlorhydria in painful conditions may persist after the pain has been completely relieved by treatment.

We have not been able to confirm Bönniger's observations with regard to gastric ulcer. In six cases, in all of which the diagnosis was confirmed by operation, four ounces of 0.5 per cent. hydrochloric acid, introduced by a tube into the empty stomach, produced no sensation whatever. The same result was obtained in another case, when a mixture of hydrochloric acid with pepsin was used. In Bönniger's cases the diagnosis does not seem to have been confirmed by operation; it may therefore have been incorrect. Our observations show that, contrary to the common belief, contact with free hydrochloric acid is not the direct cause of the pain in gastric and duodenal ulcer, although immediate relief generally follows the administration of an alkali.

The sensation of heartburn or pyrosis has often been ascribed to the regurgitation of hydrochloric acid into the œsophagus. Our observations, however, negative this theory.

We have found that 1 per cent. lactic acid and 1 per cent. acetic acid produce no sensation when introduced into the œsophagus or stomach. As the quantity present in the severest

† J. E. Schmidt. *Mitteil. aus den Grenzgeb. d. Med. u. Chir.*, xix., 278, 1909.

cases of gastric fermentation is never as great as this, these acids can also have no direct relation to the production of pain or heartburn.

III.—EFFECT OF ALCOHOL AND CARMINATIVES.

Heineke and van Selms* made some observations on the sensations produced in the throat, œsophagus and stomach by Carmelite water (a liqueur), oil of peppermint and oil of cloves. The fluid was introduced into the stomach by a tube in the case of 15 patients suffering from gastric disorders, but it was drunk in the ordinary way by the 16 normal subjects who were examined. The observations on the latter are of little value, as our experiments have shown that it is impossible for an individual to distinguish between a sensation produced in the lower end of the œsophagus and in the stomach. Moreover, only a single experiment was performed on each of the normal individuals. Of the 15 who drank Carmelite water, 12 experienced a sensation of warmth or burning which they referred to the stomach; 2 only felt a burning in the throat and 1 in the throat and œsophagus. It is not stated, however, whether in the 3 exceptional cases the liqueur was drunk after meals or on an empty stomach. The only individual who drank peppermint water had a feeling of warmth in the epigastrium.

In the case of the patients a burning sensation was experienced by all except two, whether Carmelite water, or 0.3 to 0.8 per cent. oil of peppermint or cloves was drunk. One exception was a man of 52, who had epigastric pain, hæmatemesis and melæna; possibly he had a duodenal and not a gastric ulcer. The other exception was a dyspeptic girl, who experienced no sensation when given 0.8 per cent. oil of peppermint or cloves or diluted Carmelite water; undiluted Carmelite water, however, produced a sensation of heat. Four of the 11 patients whose symptoms suggested the possibility of a gastric ulcer had a sensation of pain as well as of heat; this was not the case in any of the 4 patients who were obviously merely dyspeptic. In a good many instances it was found that the situation of the sensation moved with changes in posture. Unfortunately no diagnoses are given in the original paper, those referred to here being only what are suggested by the very imperfect clinical data given.

Becher* noticed no sensation on introducing brandy into the œsophagus or the stomach.

Our first experiments were done with crème de menthe, and in order to separate the effects of the peppermint from those of the alcohol we also used peppermint water and a solution containing 48 per cent. alcohol with 28 per cent. cane-sugar, these amounts being the same as those present in the

* Loc. cit.

liqueur. Crème de menthe, introduced by a tube into the stomach, occasionally produces an immediate sensation of warmth, but more frequently this only develops in the course of a minute or two. A similar result was obtained with the 48 per cent. alcohol, but not with the peppermint water, so that it is the alcohol, and not the peppermint, which produces the sensation after the liqueur is introduced into the stomach. Crème de menthe also produces an immediate burning sensation in the epigastrium, when poured through a tube into the lower end of the œsophagus. This is a much stronger sensation than that produced in the stomach, but it is impossible to distinguish the locality of the two. This burning sensation in the œsophagus is produced by the alcohol, as the 48 per cent. solution has the same effect, whilst the peppermint water, if warmed to the body temperature, produces no sensation. It may therefore be concluded that the immediate burning sensation produced by a liqueur is in the œsophagus, and that the subsequent feeling of warmth is in the stomach. Both are due to the alcohol alone. It was found that the lower end of the œsophagus is so sensitive to alcohol that, in testing the sensibility of the stomach, special precautions had to be taken to prevent a few drops reaching it when the tube was withdrawn. The tube was kept in the stomach for half a minute after all the fluid had been poured down, and any remaining drops were washed away by a little water before it was removed.

We have confirmed our results by observations on patients on whom a gastrostomy had been performed for epithelioma of the œsophagus. On pouring a 48 per cent. solution of alcohol by a tube into the artificial opening of the stomach a sensation of warmth was produced either immediately or after a short latent period. One patient, who had felt nothing when hot water had been introduced, although he was blind-folded and had no idea what was being done, spontaneously stated that the sensation was more like that produced by swallowing spirits than by drinking hot water, and that it could perhaps be better described as "burning" rather than merely warm. On the other hand, peppermint water produced no sensation.

In another man on whom a gastrostomy had been performed we found that the introduction of two ounces of 5 per cent. alcohol produced a definite sensation of warmth after a latent period of half a minute; the sensation gradually faded away after about three minutes. In a normal individual 25 per cent. alcohol produced a burning sensation, but 5 ounces of 1 per cent. alcohol had no effect.

Alcohol generally gives rise to no sensation when introduced into the colon through a colostomy opening. On one occasion, however, a sensation of heat was felt deeply in the abdomen. On repeating the experiment a few minutes later, no sensation was produced, probably owing to access to the mucous membrane being prevented by the mucus, which was secreted as a result of the alcoholic stimulation.

Heartburn is the hot sensation usually referred to the epigastrium, but sometimes more widely diffused, which may occur in dyspepsia. It is frequently accompanied by regurgitation of fluid, which produces a similar sensation beneath the sternum and a sensation of scalding in the pharynx. We have shown that the presence in the stomach or œsophagus of excess of free hydrochloric acid or of the organic acids, which result from fermentation in the stomach, cannot be the cause of these symptoms. The burning sensation produced by alcohol in the stomach closely resembles heartburn, and the stronger sensation it produces in the œsophagus resembles the substernal burning sensation which may accompany heartburn. It seems possible, therefore, that alcohol, which may be formed in the stomach in considerable quantity by the action of yeast and *sarcinæ* on carbohydrates, is the cause of heartburn when present in excess in the stomach, and its regurgitation into the œsophagus gives rise to the burning sensation which may be felt beneath the sternum in such cases. The scalding in the pharynx is probably due partly to alcohol, but more to the organic acids with which it is generally associated.

CONCLUSIONS.

1 The œsophagus, stomach and intestines do not possess tactile sensibility.

2. The œsophagus, but neither the stomach nor the intestines, is sensitive to thermal stimulation. The sensation of heat and cold felt in the epigastrium on swallowing hot and cold fluids respectively, is produced in the lower end of the œsophagus.

3. Hydrochloric acid in a strength greater than the maximum ever secreted by the gastric mucous membrane produces no sensation in the œsophagus or stomach, whether normal or ulcerated. Lactic and acetic acids also give rise to no sensation.

4. Alcohol produces a burning sensation both in the œsophagus and in the stomach, but not in the colon.

5. Carminatives produce no sensation in the œsophagus or stomach.

6. The pain associated with functional and organic diseases of the stomach and duodenum is not directly due to hydrochloric or organic acids.

7. It is probable that heartburn is caused by the excessive production of alcohol by fermentation in the stomach.

THE INFLUENCE OF ANÆSTHETICS ON THE BLOOD PRESSURE.

By

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(Communicated by GEORGE ROWELL.)

THE blessings conferred by anæsthesia are so many, and its usefulness so manifest, that there is some danger of losing sight of the influence of the particular agent in the general condition that it produces. That this danger is a very real one is proved by the confusion that still exists as to the best means of avoiding serious complications, and as to the best methods of remedying these complications when they arise. It was long taught that a slight degree of cyanosis during anæsthesia acted as a healthy stimulus to the respiratory and other nerve centres, and that the pulse could be safely neglected, being of little or no use as a signal of disaster. A few years ago it was common, and is by no means rare to-day, for an operator, while accepting moral and legal responsibility, to demand a degree of anæsthesia that is in itself dangerous, quite apart from the contributory effect of the surgical procedure. Until a comparatively recent date it was commonly supposed that shock could be avoided by producing a sufficiently profound narcosis, and that those cases of disaster that occurred from time to time were due to insufficiency of anæsthesia. It is now generally recognised that no depth of anæsthesia can wholly abolish surgical shock, and that in those

cases where the anæsthetic is unduly pressed there is an additional element of shock due to the anæsthetic itself.

It is, moreover, evident that anæsthetics depend, for their action, on their temporarily inhibitory effect on the nervous centres, and that it is due to their selective properties on these centres that surgical anæsthesia is possible. Fortunately the higher centres are those that are first affected, motion and sensation being stilled before the respiratory and cardio-vascular centres, or the production of anæsthesia would necessarily be fatal. It is, therefore, the responsibility of the anæsthetist to pilot his subject into the mid-channel that lies between the dangers of insufficient anæsthesia, with its liability to psychic and inhibitory disturbance, and those of deep narcosis, which may overwhelm the vital functions. It would appear that this channel of safety is wider, and the dangers on either side less insidious in the case of some anæsthetics and some methods of administration than in that of others, and it is with a view to clearing up some of these points that this paper has been undertaken.

Due, in great measure, to the excellent work of Crile on blood pressure, the opinion has gradually been gaining ground that the chief dangers of modern surgery—shock and collapse—are due to a fall in the arterial blood pressure, and are due to this cause alone. It is possible that this may be a somewhat exaggerated view, but certain it is that, though a falling arterial blood pressure may not always be the direct cause of disaster, it will always be the first sure warning of its imminence, while its rise will be the first sign of recovery.

The chief factors in the maintenance of arterial blood pressure are:—

1. The strength and regularity of the heart's action.
2. The peripheral resistance of the arterioles.
3. The elasticity of the arterial walls.

Of these three factors the first two are those which can alone be influenced by the action of the various anæsthetics, and are considered here.

The strength of the heart beat is mainly affected by the quantity and quality of the blood supplied to it by the great veins, and by reflex stimulation of the cardio-inhibitory and cardio-accelerator nerve fibres. The maintenance of the blood supply is sustained primarily by the tonic action of the vaso-motor centre, which, especially by its constricting influence on the splanchnic vessels, and, to a lesser extent, on the peripheral arterioles elsewhere, keeps the blood in the arterial system, and prevents an accumulation in the splanchnic area and the large veins. Another factor in the maintenance of the blood supply of the heart is the pumping action of respiration, which by the descent of the diaphragm, during inspiration, produces an increase in abdominal pressure, and thus forces the blood from the splanchnic area, and at the same time, by the negative pressure produced in the thorax, draws the blood towards the heart. It has been shown that this action of respiration alone is capable of driving the blood through the right heart and lungs, and that in deep abdominal breathing the rectal pressure may rise to 30 mm. hg., and frequently gives a range of 20 mm. hg., showing what an influence deep respiration must have both on the return of venous blood and on the resistance of the splanchnic area.*

Reflex stimulation of the cardio-inhibitory fibres of the vagus, causing a diminution in the rate and strength, or an actual stoppage of the heart's action, may be produced by insult to sensory nerves, especially those supplying the splanchnic area, or by direct stimulation of the branches of the vagus, such as the recurrent laryngeal in operations on the neck, and possibly by the immediate action of strong anæsthetic vapour on the afferent nerves supplying the respiratory tract. The peripheral resistance of the arterioles is maintained by the tonic action of the vaso-motor centre, and this action is increased by stimulation of sensory nerves; over-stimulation may, however, produce exhaustion, and is the main factor in the production of surgical shock.†

* Leonard Hill, "Further Advances in Physiology."

† Crile, "Blood Pressure in Surgery."

It will be evident from the consideration of these two factors that they are interdependent—that the heart relies upon the tonic constriction of the peripheral arterioles for its blood supply, while the vaso-motor centre fails to perform its function unless it is fed by a sufficiency of arterial blood. It follows, therefore, that any marked diminution in the efficiency of either one may produce a vicious circle, which, if unremedied, must sooner or later bring about a progressively serious fall in blood pressure.

It would be well at this point to consider the various conditions that are comprised under the terms Syncope, Shock, and Collapse, as being the three states characterised by a serious fall in the arterial blood pressure. In so doing, the classical experiments of Crile are taken as a foundation of the conclusions arrived at.

Syncope is the name used for a sudden and usually temporary cessation, or serious enfeeblement, of the vital processes through cerebral anæmia. It is, in the majority of cases, of reflex origin, and due to cardiac inhibition, generally the outcome of insult to the sympathetic, especially in the splanchnic area, or to sensory nerves, such as those supplying the larynx, the testicle, or anal region. Syncope may also follow a sudden change of position, *e.g.*, from the horizontal to the sitting, or from the Trendelenberg to the horizontal, owing to the fact that during anæsthesia the mechanism for the compensation of the effect of gravity is frequently in abeyance.

Shock is due to an exhaustion of the vaso-motor centres usually following over-stimulation. It is frequently caused by the same conditions as syncope, and is the effect of their prolonged exhibition, generally in long and severe operations. It may also follow an insufficient supply of blood to the centres in cases of severe hæmorrhage, or its toxic properties in respiratory obstruction. It may, moreover, be the direct outcome of the anæsthetic circulating in the blood which supplies the brain, and be due to a prolonged administration or to too high a saturation: while it may be directly attributable to loss of heat

from the surface. Shock is usually somewhat gradual in its onset, and may be caused by one or more of the foregoing factors.

By collapse we signify a serious fall of blood pressure occurring more suddenly than in shock, and "due to a suspension of the function of the cardiac or of the vaso-motor mechanism, or to hæmorrhage."* It is specially prone to occur in cases of sudden and severe hæmorrhage, injuries to the brain and spinal cord (particularly in the region of the important centres) and in too high a percentage of anæsthetic vapour circulating through the cardiac chambers.

The deductions arrived at in this paper are drawn from the notes taken during 140 administrations; the blood pressure was estimated every five minutes, or more often every two and a half minutes, by means of a Riva Rocci sphygmomanometer. The records were made, in every case but one, from the arm placed in the same horizontal plane as the apex beat; in the remaining case the observation was made from the leg. The blood pressure recorded is the systolic, and is the pressure required to obliterate the radial pulse at the wrist. The normal blood pressure was taken when possible, and in the great majority of cases either twenty-four hours before the operation, or more often ten days after. The first observation during the administration was usually made immediately light anæsthesia was established, the duration of the administration being reckoned from the time that the anæsthetic was first applied.

Chloroform was the sole anæsthetic agent used in 15 cases, while in 2 others A.C.E. mixture was given for a few minutes at the commencement. In all of the 17 cases a fall of arterial blood pressure below normal occurred at some period of the administration; the extent of the fall was in most cases considerable (averaging 35mm. hg.), and was usually in direct proportion to the depth of the anæsthesia.

The following is a list of the cases, with some of their main features:—

* Crile, "Blood Pressure in Surgery."

Initials and Age.	Operation.	Length of Administration.	Blood Pressure in m.m. Hg.		PULSE.				General Condition, etc.	
			Normal.	Lowest Record.	Normal.	Slowest Record.	Rate.	Average Regularity.		Strength.
I. L., 37	For cysts in epididymis	50 min.	132	92	72	52	Slow	Regular	Small	Sudden fall of blood-pressure at end of administration.
F. C., 67	Exploratory laparotomy	55 "	145	50	80	60	Variable	Irregular	Small	Slight syncopal attack early and late.
N. W., 29	Exploratory laparotomy	35 "	122	102	92	92	Quick	Regular	Good	Straining and rigid throughout.
A. F., 51	Gastrojejunostomy. Perforated gastric ulcer	90 "	?	98	92	68	Slow	Irregular	Small	Syncopal attack at end, when blood-pressure fell very low temporarily.
M. N., 48	For hernia ...	50 "	145	110	86	60	Slow	Regular	—	Light anæsthesia.
C. M., 25	Ovariectomy ..	50 "	120	104	68	80	Quick	Regular	—	Light anæsthesia.
W. P., 26	For fractured olecranon	55 "	115	112	64	46	Slow	Regular	—	Rigid throughout.
E. S., 24	For double hernia ...	60 "	120	90	68	60	Medium	Regular	—	Blood-pressure fell markedly when anæsthetic was pressed.
H. C., 60	Excision of growth in abdominal wall	60 "	?	110	?	72	Medium	Irregular	—	Light anæsthesia. Normal blood-pressure, probably 140-150.

Initials and Age.	Operation.	Length of Administration.	Blood Pressure in m.m. Hg.		PULSE.				General Condition, etc.
			Normal.	Lowest Record.	Normal.	Slowest Record.	Rate.	Average Regularity. Strength.	
V. P., 31	Appendicectomy ..	47 min.	110	90	68	72	Medium	Regular	Very light anaesthesia.
L. S., 21	Appendicectomy ...	50 "	120	102	84	84	Quick	Irregular	Light anaesthesia. Syncopal attack when anaesthetic pressed.
T. O., 45	Appendicectomy ...	65 "	125	100	72	60	Slow	Irregular	Syncopal attack early. Blood-pressure fell when anaesthetic pressed.
W. A., 18	Exploratory for cerebellar tumour	60 "	118	78	84	40	Slow	Irregular	Syncopal attack when dura mater was opened.
J. W., 38	Resection of nerve for painful stump	42 "	125	90	70	48	Slow	Regular	Considerable rigidity throughout.
T., 57	For epithelioma of lip	60 "	152	108	84	68	Medium	Irregular	Early syncopal attack before incision.
C. S., 12	For hernia ...	45 "	102	100	64	64	Quick	Regular	Rigid throughout.
A. M., 27	Opening shoulder ...	42 "	116	58	74	60	Slow	— Small	Late syncopal attack.

The fall in the blood pressure usually commenced quite early—in the majority of cases before the incision was made, and was accompanied with quiet respiration, usually some pallor, and a slow soft pulse.

In the five cases enumerated above where the fall of blood pressure did not exceed 20 mm. hg., the anæsthesia was very light, and there was some movement or rigidity during the greater part of the administration.

In 3 of the 17 cases the mean blood pressure, calculated from the whole curve during administration, was above the normal for the individual ascertained ten days later, and in 2 others was approximately normal; in the remaining 12 cases it was below normal. In every case in which this mean blood pressure was not below normal, the anæsthesia was extremely light.

In addition to the 17 cases already mentioned, there were 8 others in which chloroform was given for a considerable time, giving a total of 25. Of these 25 cases, 10 showed evidence of some degree of syncope or collapse during the administration, the pulse for a few seconds becoming almost or quite imperceptible. In the majority of these, the condition appeared to be directly due to the toxic effect of the anæsthetic, and to follow an increase in the depth of narcosis, while in the remainder the anæsthetic effect was only contributory. In one of these latter cases the immediate cause of the syncopal attack was movement from the Trendelenberg to the horizontal position, the loss of the aid of gravity, which was thus involved, being sufficient to temporarily upset the circulatory equilibrium, while another similar attack followed a few minutes later, and directly preceded vomiting.* These two attacks were the outcome of splanchnic stasis, which is one of the principal dangers of prolonged chloroform anæsthesia, owing to its inhibitory action on the vaso-motor and respiratory centres, and the consequent loss of tone in the vessels of the splanchnic area, coupled with the diminution in the propulsive influence of respiration on the circulation.

* See Chart 6.

In 8 of the 25 cases, alcohol was given with the chloroform (1 in 10), and though there was invariably a fall of blood pressure below normal, the extent of the fall and the tendency to syncopal attacks appeared to be less than in those in which chloroform was given alone. This would support the conclusions of Schafer and Scharlieb that alcohol lessens the depressing effect of chloroform, but it seems to be doubtful whether this is due to any alleged stimulating property of alcohol, or merely

F. C., 67. EXPLORATORY LAPAROTOMY.

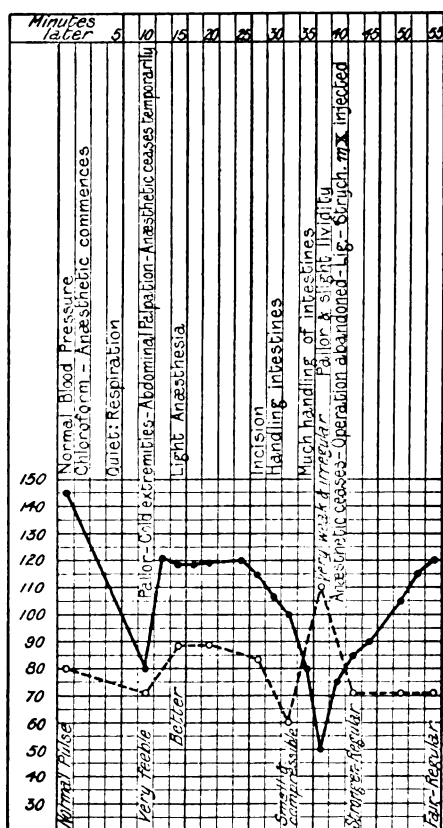


CHART 1.—This illustrates the initial fall during chloroform anæsthesia with quiet respiration, pallor and slow pulse; also the rise of blood pressure as anæsthesia became lighter, with the rapid fall and threatened collapse following manipulations in the splanchnic area.

to the fact that the chloroform vapour is diluted and therefore less potent. As with pure chloroform, increase in the depth of the anæsthesia invariably produced a distinct fall in blood pressure. Taken in the aggregate, the cases in which alcohol was given with the chloroform would appear to have been marked by a greater tendency to excitement and struggling during light anæsthesia, and a diminished frequency of marked irregularity and slowing of the pulse; respiration, moreover, was, on the whole, less depressed, while perhaps the most marked characteristic of these cases over those of pure chloroform anæsthesia was the absence of the larger variations in the blood pressure after anæsthesia had been established. All of these features would indicate a more gradual onset and a lessened depth of anæsthesia, and would suggest the advisability, in those cases where chloroform is the anæsthetic of choice, of administering it in such a way that the strength of the vapour can be easily regulated.

The anæsthetic given was A.C.E. mixture in 23 cases, in 21 of which the blood pressure fell below normal during the administration. While in 7 (30 per cent.) the average blood pressure was above normal, the remaining 70 per cent. had an average blood pressure below normal. The average maximum fall of blood pressure was equal to about 30 mm. hg., slightly less than that occurring with chloroform, but in other respects was similar to it, and was ushered in with the same symptoms, and promoted by the same conditions.

There was a greater tendency towards respiratory obstruction during A.C.E. administration than with pure chloroform, and consequently the effect of air deprivation was more marked, and its influence on blood pressure more easily estimated. There were in all 8 cases of A.C.E. administration in which respiratory obstruction occurred, and in 7 of these the average blood pressure was below normal, while the only case in which it was slightly above normal was one in which a very high blood pressure had previously been maintained under ether, the administration of A.C.E. for half an hour being accompanied

with a considerable fall. Of the remaining 15 cases in which no respiratory obstruction occurred, 6 had an average blood pressure above normal, while 9 had a blood pressure below normal. In the only 2 cases out of the 23 A.C.E. administrations in which the blood pressure remained above normal throughout, the anæsthesia was light and the colour good.

It would appear, therefore, that during the administration of A.C.E., cyanosis and respiratory obstruction have a markedly depressing effect on the circulation. In examining these cases it is seen that a fall of the average blood pressure (that is, a considerable fall, and one not merely due to a passing cause) is nearly three times as common in cases where respiratory obstruction occurs as it is in those where a good colour is preserved throughout.

In three of the administrations collapse occurred early, before the operation commenced; in all of these cases, before actual collapse supervened, there was marked pallor, respiration became very quiet and shallow, pulse slow, compressible and irregular, while the blood pressure at first gradually, and later very rapidly, fell, the pulse finally becoming imperceptible. In each case the respiratory movements were very feeble and irregular, and in two actually ceased. Strychnine was injected in all, artificial respiration performed in two, and, after a short interval, in which no anæsthetic was given, open ether was substituted, and the administration continued without further trouble. In one of these cases, after twenty minutes of open ether, during which the blood pressure had been steadily rising, A.C.E. mixture was once more used in very small quantities, with the result that in less than ten minutes the blood pressure fell considerably, and the pulse once more became small and compressible; the anæsthetic was again changed to open ether, when the pulse improved and the blood pressure rose in a few minutes to slightly above normal.*

A mixture of chloroform and ether (1 : 2) was given by the open method in five cases, and was attended with a considerable

* See Chart 2.

A. B., 27. APPENDICECTOMY.

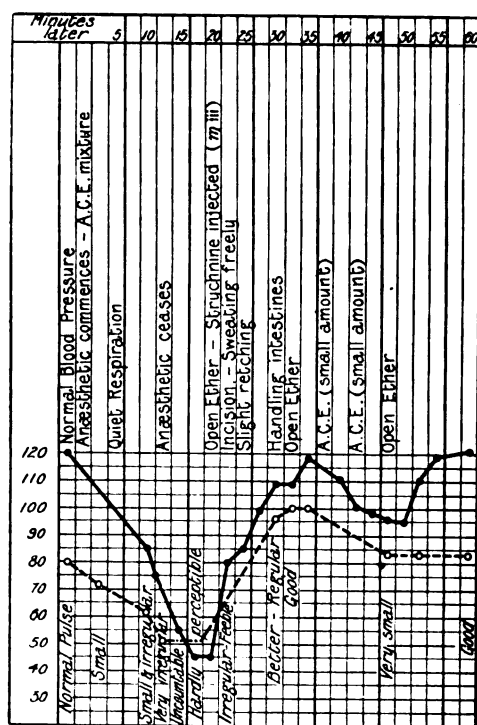


CHART 2.—Showing the fall of blood pressure under A.C.E., and collapse before incision, with rise of blood pressure during ether administration.

fall of blood pressure in each. The administrations of this mixture are too few in number to draw any exact conclusions from, but the inference is that the general effect on blood pressure is much the same as under chloroform and A.C.E. mixture. In two cases where it was given, once with ohloroform, and once with A.C.E., it would appear that the depressing effect was slightly less marked than that of chloroform, and slightly more than that of A.C.E. mixture.

Ether was the anæsthetic used in 60 cases, the duration of the administration being from 25 minutes to $1\frac{1}{2}$ hours. Of these 60 cases, 7 had morphia administered before the operation commenced, and are considered separately.

Of the remaining 53 ether cases, 47 (89 per cent.) had an average blood pressure above normal, 2 more cases having an average blood pressure equal to normal, and only 4 (less than 8 per cent.) had an average blood pressure below normal.

There were 37 cases in which the blood pressure remained above normal during the whole administration, and 2 more in which it never fell below normal, which gives a percentage of nearly 74 of those cases whose blood pressure never became sub-normal.

There were in all 14 cases (26 per cent.) in which the blood pressure fell below normal; in the majority of these cases the fall was slight and of short duration, and could not in any one be attributed directly to the anæsthetic. Of the above 14 cases only 5 had any considerable fall (i.e., more than 10mm. hg.), which was directly due to shock in 4 cases, and to severe hæmorrhage in the one, while in two of the cases in which shock appeared to be the principal factor there was considerable hæmorrhage, and in every case there was respiratory obstruction.

It is noteworthy that in every one of the 53 ether administrations there is an initial rise of blood pressure, i.e., before incision. The rise might obviously be the result of various causes, such as excitement, struggling, and respiratory obstruction, and cannot be accredited to the action of the anæsthetic alone. It is, however, admissible to contrast the action of chloroform in this respect, where in every case in which it was given alone there was an initial fall of blood pressure. It would appear reasonable to connect these facts with the tendency to syncope and collapse in the early stages of chloroform anæsthesia, and with its absence during the same period of ether administrations.

The effect of respiration and of respiratory obstruction on the blood pressure is very marked during ether anæsthesia, and apart from severe shock and hæmorrhage, and the temporary action of violent struggling, excitement, and vomiting, would appear to be the main factor in its determination.

Respiratory obstruction of varying degree occurred in 33 of the cases, whereas absence of respiratory embarrassment with good colour is noted in 20. Of the 37 cases in which the blood pressure was above normal throughout, 18 (or practically half) had no respiratory obstruction; while of the 14 cases in which the blood pressure fell below normal, 12 had respiratory obstruction, and in the 2 cases in which there was no obstruction, the blood pressure generally was considerably raised, and only fell temporarily, and from an obvious and very definite cause. In the one case, the fall, of 5 minutes' duration, was due to the actual removal of the breast, and was only equal to 5 mm. hg., while in the other, ether had been administered for 45 minutes with a continuously raised blood pressure, when the patient was suddenly moved to a semi-sitting posture, the blood pressure immediately falling 15 mm. hg.*

Of the 47 ether cases in which the average blood pressure was above normal, 27 had some degree of respiratory obstruction, while in 20 (rather less than half) breathing was unembarrassed throughout, and the colour good. In the 4 cases in which the average blood pressure was below normal, and in 2 more in which it was about normal, there was respiratory obstruction in each instance.

There were 11 of the 53 ether cases in which the open method alone was employed without the previous administration of morphia. It was found impossible to base any very definite conclusions on so small a number as to the comparative influence of the two methods (close and open) on the blood pressure. It may, however, be said that in the open method there is a smaller incidence of respiratory obstruction, and that when present it is usually less in degree. As a natural sequence, it may further be said that there is less frequently a large rise of blood pressure at the commencement of an administration, which is so often due to a temporary embarrassment of respiration, the level of pressure is less inclined to fluctuate, and the tendency to fall at the end of a long and severe operation is less marked.

* See Chart 7.

Of the series of 53 ether administrations there were 19 in which the duration was for one hour or more. In the following table some of the chief points that affect blood pressure are enumerated, the cases taken being of sufficient length to determine the ultimate results of the various factors as well as the more temporary and sometimes misleading effects:—

Initials and Age.	Operation.	Mode of Administration.	Duration.	Respiration and Colour.	In m.m. of Hg.			
					Normal B.P.	Max. B.P.	Min. B.P.	Fluctuation of B.P.
A.F. 41	Excision of breast and removal of cervical gland	Closed	75 min.	Much cyanosis	120	155	110	45
A.R. 52	Radical cure of umbilical hernia	Closed	65 "	Much cyanosis	140	180	110	70
J.W. 19	For severed ulnar nerve	Closed	60 "	Cyanosis	118	170	130	40
L.G. 27	Ovariectomy and appendicectomy	Closed	85 "	Good	105	138	128	10
E.B. 34	Ovariectomy	Closed	75 "	Early resp. obstn.	115	162	108	54
G.R. 20	Cystoscopy and sequestration	Closed	75 "	Slight resp. obstn.	120	150	105	45
K.G. 22	Appendicectomy	Closed	85 "	Slight cyanosis	108	150	108	42
E.D. 35	Excision of mural fibroid	Closed	90 "	Respy. obstn.	115	130	92	38
A.P. 25	Ovariectomy	Closed and open	65 "	Slight resp. obstn.	118	140	115	25
H.H. 32	Amputation of leg	Closed and open	65 "	Cyanosis	114	145	108	37
M.W. 59	Ovariectomy	Closed and open	75 "	Cyanosis	125	152	115	37
L.H. 20	Excision of gut and anastomosis	Open & closed	75 "	Good	112	148	120	28
F.B. 12	Appendicectomy	Open	65 "	Good	106	137	115	22
E.S. 36	Ovariectomy	Open	75 "	Good	122	140	132	8
G.P. 39	Radical cure of varicose veins	Open	75 "	Respy. obstn.	120	135	92	48
F.McC. 12	Removal of vesical calculus (ventrally)	Open	70 "	Good	100	125	112	13
C.C. 30	Removal of uterine fibroid	Open	75 "	Respy. obstn.	120	148	90	58
A.J. 18	Radical cure of hydrocele	Open	60 "	Good	122	140	126	14
J.B. 52	Gastrojejunostomy	Open	70 "	Slight resp. obstn.	118	122	104	18

In 6 of the above cases, in which there was no respiratory obstruction, and in which the colour is noted as being good throughout, the average fluctuation of blood pressure (*i.e.*, the difference between the maximum and minimum recorded) was equal to 16 mm. hg., the greatest fluctuation being equal to 28 mm. hg. Of the 13 in which varying degrees of respiratory obstruction were noted, the average fluctuation was equal to 43 mm. hg. Of the 6 cases with good colour throughout, the average blood pressure was equal to 20 mm. hg. above the normal. Of those cases with respiratory embarrassment, the average blood pressure was equal to 4 mm. hg. above normal, the highest average being 30 mm. hg. above and the lowest 20 mm. hg. below normal blood pressure.

Of the 6 cases in which the colour was good throughout, the blood pressure never once fell below normal during the administration, while of the 13 cases in which respiratory obstruction of varying degree was noted, 11 at some time or another showed a fall below normal, and in the 2 remaining cases the obstruction was only slight and quite temporary.

The fluctuation in the blood pressure of those cases with respiratory obstruction was, on the average, nearly three times as great as in those where the breathing was unhampered, the amount of the fluctuation being, as a rule, in direct proportion to the amount of embarrassment; the fluctuation, moreover, comprised an initial rise of blood pressure, and in a large majority of cases was followed by a fall below normal. This fall below normal did not occur in any of those cases where breathing was unimpeded, neither were they marked by the large initial rise, the main feature being an even pressure that was throughout slightly above normal.

In 10 cases of ether administration the blood pressure was taken the morning after the operation, and was found in every instance to be above normal; this would appear to indicate that post-operative shock, as a consequence of over-stimulation by ether, was at any rate an unusual occurrence.

L. G., 27. OVAROTOMY AND APPENDICECTOMY.

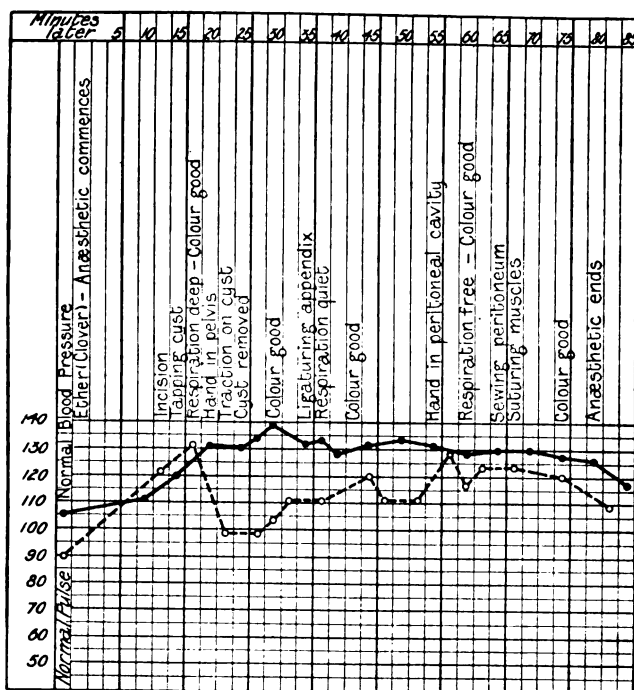


CHART 3.—Showing the effect of ether anæsthesia with unobstructed breathing.

Morphia was administered subcutaneously in 7 cases about an hour before the operation, open ether being the anæsthetic selected in each case; in 1, however, A.C.E. mixture was given during the greater part of the administration, owing to considerable respiratory obstruction and cyanosis, and in this case there was very serious collapse. The dose of morphia was one-sixth grain in 5 of the cases, and one-fourth grain in 2. In 4 of the 7 cases the blood pressure fell below normal, and in 3 of these the average blood pressure was below normal; the depression was, moreover, a considerable one. In all the 4 cases the fall of the blood pressure was due mainly to shock, though, in addition, 2 of the cases had marked respiratory

A. R., 52. RADICAL CURE OF UMBILICAL HERNIA.

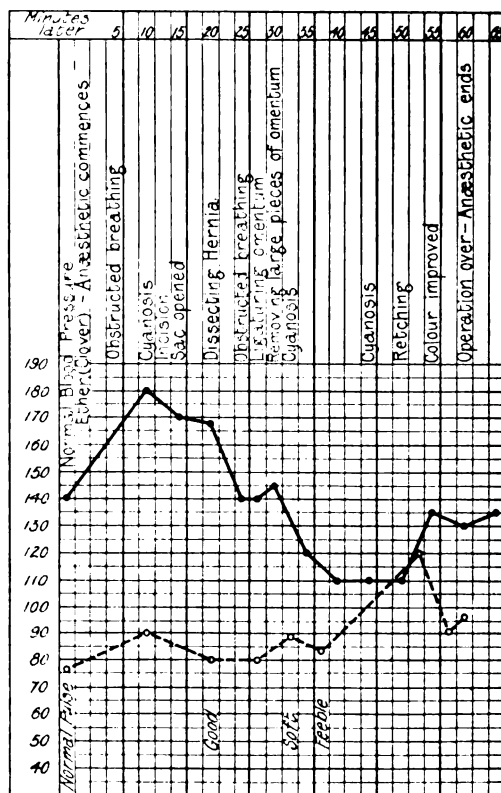


CHART 4.—Showing the effect of obstructed breathing and cyanosis during ether anæsthesia.

obstruction, and in one of these latter there was some hæmorrhage. Two further cases, in which the average blood pressure was above normal during the administration, showed a fall below normal a few minutes after the anæsthetic ceased. The cases in this series are too few to draw any definite conclusions from, but would appear to suggest that the value of morphia injections before operation for the prevention of shock is extremely doubtful. It is probable that the depressing effect of morphia on respiration would indirectly tend to produce a fall of blood pressure, and would more than counteract the conservative

influence of the drug on the vaso-motor centre following its supposed isolation from sensory impulses. Taken as a whole, the operations in this series were not of unusual length or severity as compared with those in which ether alone was administered, whereas the difference in the level of the blood pressure was considerable, the influence of shock very marked, and the effect of embarrassment of breathing appeared to be more rapid and of greater extent; the latter result being, no doubt, due to the fact that the respiratory centre was rendered less capable of responding to the usual stimuli. The depressing effect of morphia on the respiratory centre would seem likely to produce an additional element of danger in those cases where chloroform is the anæsthetic used.

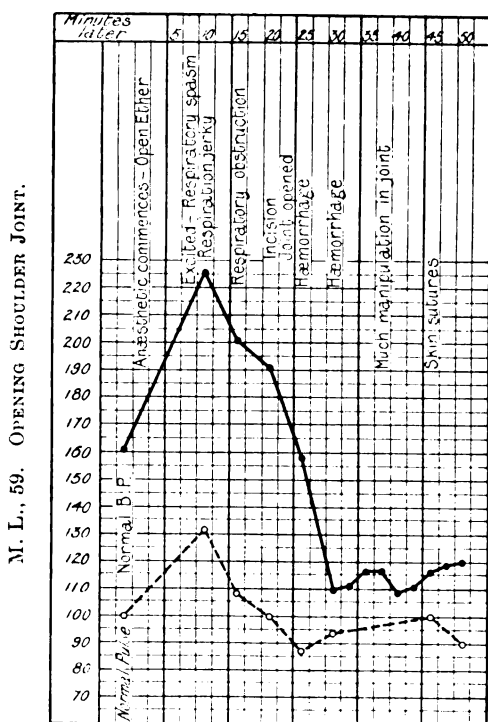


CHART 5.—Illustrating the effect of morphia during ether anæsthesia with respiratory obstruction.

Table of cases in which morphia was administered before operation :—

Initials and Age.	Operation.	Duration	Respiration and Colour.	B.P. in m.m. Hg.				General Condition, etc.
				Normal.	Max.	Min.	Average.	
W. E. 15	Opening shoulder	40 min.	Obstructed. Congested	102	132	108	116	Condition good; only slight respiratory obstruction.
M. H. 41	Hysterec- tomy (ventral)	100	Obstructed. Cyanosis	94	132	50 & ?	?	A.C.E. given for some time. Much shock.
A. C. 31	Hysterec- tomy (vaginal)	40	Free. Good	112	146	104	115	Much shock.
M. L. 59	Opening shoulder	50	Obstructed. Cyanosis	164	226	110	116	Much shock and some hæmorrhage.
C. W. 57	Exploratory laparotomy	42	Free. Good	108	110	70	80	Much shock in cachectic subject.
S. P. 60	Excision of knee	40	Free. Good	122	156	126	130	B.P. fell to 98 ten minutes after anæsthetic ceased.
A. B. 45	Radical cure of varicose veins	35	Obstructed. Congested	130	156	118	135	B.P. fell slightly below normal 5 minutes after anæsthetic ceased.

"When a large hutch rabbit is held up for a few minutes with its limbs stretched out and head uppermost, it may become unconscious and die of cerebral anæmia. The blood collects in the flaccid abdomen, the animal not being able to return it to the heart by changing its posture. A wild rabbit with taut abdomen is not affected in this way." "The wild rabbit can, however, be brought into like state by a dose of chloral, and so can a dog by chloroform poisoning or bleeding."* The

* Leonard Hill, "Further Advances in Physiology."

effect of anæsthesia in man is precisely the same, varying only in degree with the depth of narcosis and with the agent employed to produce it. For the time being the mechanism for preserving circulatory equilibrium is in abeyance, and as a direct consequence of this any very sudden or violent movement during anæsthesia is apt to bring about a rapid fall of blood pressure. This effect is especially marked during chloroform administrations, and may then occur under quite light anæsthesia. Speaking generally, it may be said that any position which, owing to the force of gravity, promotes the flow of blood towards the heart and cerebral centres, tends to raise the blood pressure, while a position with the opposite influence has the reverse effect. Under chloroform the latter tendency is always imminent, and a severe fall of blood pressure may follow quite a slight diminution in the relative value of the posture employed. The fall is due to cerebral anæmia, with consequent inhibition of the vaso-motor centre, and loss of the tonic contraction of the vessels in the splanchnic area, leading to a condition of stasis in the large venous reservoirs of the abdomen. As a rule, the fall of blood pressure, though severe, is of short duration, other factors quickly coming into play and rousing the vaso-motor centre to activity. If, however, the anæsthesia be too deep, or the centre in a state of exhaustion from shock, recovery may be impossible.

In the charts of two cases, produced below, the effect of change of position is seen first during chloroform, and secondly during ether anæsthesia; the effect of the Trendelenberg position is somewhat obscured in the first case, as the anæsthetic was changed at the same time from A.C.E. mixture to chloroform, and immediately followed a period of much excitement and some respiratory obstruction. The influence of the posture was apparently to contribute to the maintenance of a good level of blood pressure during a long and very severe operation.

The effect of chloroform on the blood pressure was invariably to depress, and to a slightly less extent the same result occurred under A.C.E. An increase in the depth of anæsthesia during

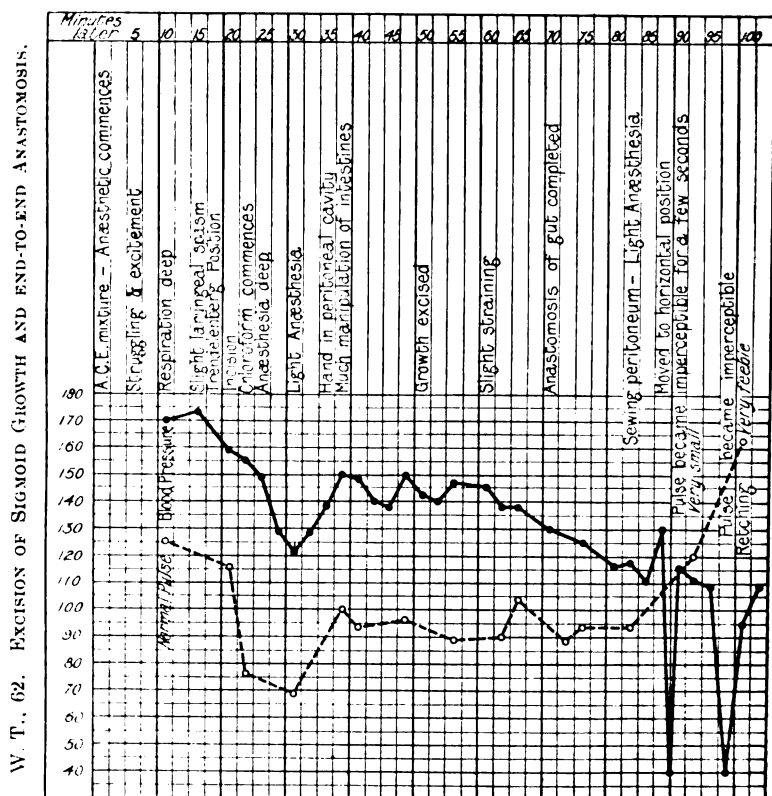


CHART 6.—Shows sudden fall occurring when the patient was moved to the horizontal position, and also the fall immediately preceding an attack of retching: in each case the pulse became almost imperceptible for a few seconds, subsequently becoming very rapid, an indication of effort on the part of the organism to restore the fallen blood pressure and to maintain the cerebral circulation.

their administration was always accompanied with a fall in blood pressure, while a diminution in depth produced the opposite result. It may, therefore, be assumed that those agents whose anæsthetic properties depend wholly or mainly upon chloroform vapour have a definite depressor effect on the blood stream. Pohl has shown* that the blood of a dog circulating during

* Hewitt's "Anæsthetics."

(i. R., 20. CYSTOSCOPY AND SEQUESTRATION.

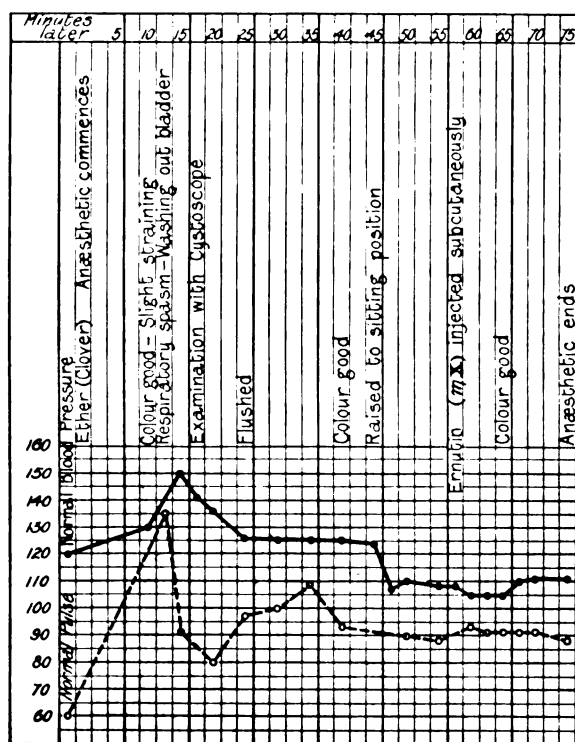


CHART 7.—Shows sudden fall occurring under ether administration when the posture was changed from the horizontal to the semi-sitting: the fall is slight, with no alteration in the pulse rate, which would appear to indicate that the cerebral circulation was not sufficiently interfered with to justify the organism in calling out its reserves. Ernucin was injected experimentally in this case, but would seem to have had little or no effect on blood pressure.

chloroform anæsthesia contained from .01—.06 per cent. of the drug. Sherrington and Sowton* have shown that chloroform in Ringer's saline solution at a strength of 300 mgs. to the litre (equal to .03 per cent.), when perfused through an isolated heart will produce paralysis in about 90 seconds: this paralyzing effect occurred sooner and was more permanent when all air and oxygen were driven from the solution, and when it was shaken

* British Medical Journal, July, 1906, p. 85.

up with CO_2 , and delivered under CO_2 . According to Pohl, this dangerous percentage of chloroform in the blood would be about the average during chloroform anæsthesia, and during irregular respiration might easily be exceeded in the blood passing directly to the heart. It has, however, been shown that chloroform in saline solution has a more toxic effect than when in solution in the blood, as it would appear to enter into some loose combination with the latter, while the isolated heart would obviously possess less resisting power than one in its normal environment. Be this as it may, it will be evident that a very slight concentration of chloroform in the blood passing to the heart would have a rapidly paralysing effect on the cardiac muscle, especially if there was embarrassment to the respiration, and a large increase in the CO_2 content of the blood.

It has been further shown by Sherrington and Sowton that at the above concentration (300 mgs. to the litre), chloroform in Ringer's saline with CO_2 , made to circulate through the vessels of an isolated limb, produced primarily a slight vaso-constriction, and a diminution in the flow of fluid through the vessels for several minutes, and that this was not followed by an increase in the flow; moreover, it is not until concentrations of over .05 per cent. are used that a vaso-dilatation is produced. It is, therefore, probable that the vaso-dilatation found during chloroform narcosis, when due to the direct action of the drug, is the result of its toxic effect on the vaso-motor centre, for it is unlikely that a concentration in the circulating blood, sufficient to produce vaso-dilatation by direct action on the vessel walls, could be reached without producing cardiac paralysis.

The depressing effect of chloroform on the vaso-motor centre is brought about directly by the inhibitory action of the drug, and secondarily through exhaustion of its vital properties consequent upon insufficiency in the quantity and quality of its blood supply. It has been estimated* that during anæsthesia by chloroform and ether the respiratory exchanges are reduced 40 per cent., and that the inhibitory effect of chloroform on physiological processes is seven or eight times as great as that of ether.

* Hewitt's "Anæsthetics."

During chloroform anæsthesia the CO_2 content of the blood is greatly increased, owing to lessened exchange, coupled with a diminution in respiratory movements. The inhibitory action on nervous and muscular tissues possessed by chloroform prevents the reply of the respiratory and circulatory systems that should follow the increased CO_2 content of the blood, and a progressively vicious circle is the natural consequence. It is, therefore, evident that during chloroform anæsthesia any degree of asphyxia must be fraught with grave danger, and the risk of its onset considerably increased by the absence of the usual reflexes.

In the early stages of chloroform administrations it is probable that the chief danger lies in its paralysing effect on cardiac muscle, which is evidenced, as anæsthesia develops, by the slow feeble pulse, with frequent irregularity of the heart's action, and a more or less rapid fall of blood pressure. Another possible cause of a rapid fall of blood pressure with similar circulatory symptoms may occasionally, at this period, follow excitation of the cardio-inhibitory centre through irritation by the chloroform vapour of the vagus nerve-endings in the respiratory tract, or of the cardio-inhibitory centre directly through the chloroform circulating in the blood.

In 11 of the 25 cases in which chloroform was given, the pulse became irregular, usually quite early in the administration, while in more than half the cases an abnormally slow and feeble pulse was noted. In the 23 A.C.E. administrations an almost identical proportion of cases were affected in this way, more than half showing considerable disturbance in the heart's action. In 8 out of the 48 cases, in which either chloroform or A.C.E. were administered, there was a serious fall of blood pressure quite early, usually before the incision was made; in each case the fall in blood pressure was preceded by a slow feeble pulse, and in six there was marked irregularity. In the course of collecting material for this paper it has been my misfortune to witness two deaths during anæsthesia. Both occurred in the early stages of chloroform narcosis, before the

incision was made, and before it was possible to make any exact observations on the blood pressure. The one death was due to the directly paralysing effect of the chloroform on the heart muscle, and the other, in an exceedingly muscular man, to respiratory spasm followed by sudden cardiac failure. In both of these cases the depressing action of chloroform on the heart was responsible for death.

In the later stages of chloroform anæsthesia, vaso-motor exhaustion becomes more prominent in its influence on blood pressure; at this stage a serious fall is usually accompanied by an increase in the rate of the pulse, an effort on the part of the heart to maintain the blood pressure and the all-important cerebral circulation. The possibility of paralysing the heart is still present, and would probably attend an even smaller percentage of chloroform, but at this period the drug is more evenly distributed through the tissues of the body, with the result that anæsthesia requires a less concentrated vapour, while the psychic element is absent. The danger now becomes one rather of exhausted nerve centres, with consequent relaxation of the peripheral vessels and engorgement of the veins in the splanchnic area, the arterial system gradually emptying itself into the large venous reservoirs of the abdomen. At this stage, too, the increase in the viscosity of the blood, which invariably takes place, must add considerably to the work of a heart already enfeebled by an insufficiency in the quality and quantity of its blood supply.

The effect of ether administration was in every case an initial rise in the blood pressure; this initial rise was greater in those cases where there was respiratory obstruction, but in these cases was invariably followed by a considerable fall of blood pressure, unless the administration was of very short duration. In those cases where no early excitement, and especially where no respiratory obstruction occurred, the initial rise was smaller in extent, but was not followed by any marked fall unless due to causes other than the anæsthetic, such as shock or hæmorrhage. In the case of ether, an increase in the

depth of anæsthesia, within certain limits, appeared to raise the blood pressure. It may, therefore, be concluded that ether possesses an intrinsic pressor action on the arterial blood stream, and that on this property depends the relative safety of its administration as compared with chloroform; this is particularly the case in the early stages of an operation where the dangers of chloroform are so very marked. It is noteworthy that in 36 administrations in which ether was given in sequence with chloroform, or A.C.E., or both, the blood pressure invariably rose under ether and fell under chloroform and A.C.E.

The pressor action of ether apparently depends on its stimulating influence on the heart and respiration; it is probable that it has little or no direct action on the vaso-motor centre, though it would appear to cause some vaso-dilatation in the peripheral vessels of the cutaneous area. In those cases where there is respiratory embarrassment, the increased CO_2 content in the blood would possibly act as a stimulus to the vaso-motor centre, but this effect is invariably followed by a correspondingly severe fall. The property that ether certainly possesses of preventing shock in severe operations would appear to depend upon its augmentor effect on heart and respiration, by which it ensures a sufficiency of arterial blood to the vaso-motor centre, rather than upon any direct stimulating action on that centre. Moreover, splanchnic engorgement, and hence the full effect of shock, is prevented during ether administration so long as increased respiratory movements occur, and this is so unless the respiratory centre is exhausted as a result of pulmonary embarrassment, or as part of a general collapse from excessive hæmorrhage or surgical shock.

With chloroform, on the other hand, the influence on the vaso-motor centre is actively inhibitory, while it has no compensating action on respiratory and cardiac functions, but by its depression of these still further reduces the vaso-motor capital, and by its limitation of diaphragmatic movement, and the general relaxation of the abdominal muscles, favours the onset of splanchnic engorgement.

The effect of ether on the pulse was invariably, unless complicated by hæmorrhage or shock, to increase its force and frequency, the effect of chloroform being to diminish the force, and in more than half the cases to diminish considerably the frequency during some part of the administration.

In 14 cases in which chloroform or A.C.E. were administered the pulse to respiration ratio was estimated, and was found to be, on the average, 3 : 2; in 31 cases of ether administration the ratio was 3 : 1. This increase in the respiratory ratio under both is probably due to the lessened exchange of gases that occurs in the lungs during anæsthesia, the comparatively much greater increase under chloroform being due to the shallowness of the respiratory movements. It would, therefore, be unwise to attach any greater significance to it, than that it is an indication of a greater disturbance in the general economy, and of serious limitation in respiratory movement. Moreover, the increased output of heart and lungs that occurs during ether administration is evidence that the organism is alive to the necessities that anæsthesia entails, while the diminution of output that accompanies chloroform narcosis further demonstrates its inhibitory tendency.

Anæsthesia was induced by spinal injection in 17 cases, stovaine being used in 4, tropacocaine in 13 instances. The following is a tabulated list of the cases :—

Initials and Age.	Operation.	Analgesic and Dose.	Pulse.			Blood pressure in m.m. Hg.			Condition, etc.
			Normal	Slowest Record	Rhythm	Normal	Min.	Max.	
W. P., 21	Appendicectomy	Stovaine, 10 cgrs.	88	56	Regular	125	98	27	Nausea and pallor.
A. D., 37	For displaced semi-lunar cartilage	Stovaine, 5 cgrs.	68	62	Regular	116	110	6	Tremors.
X., 40	Radical cure of hydrocele	Stovaine, 9 cgrs.	72	60	Regular	130	120	10	Some pain.
W. D., 16	For hernia	Tropacocaine, '022 gms.	70	64	Regular	112	96	16	
J. C., 39	For hernia	Tropacocaine, '033 gms.	76	66	Regular	112	76	36	Slight lividity, pallor, thirst.
E. P., 24	For hernia	Tropacocaine, '022 gms.	60	44	Irregular	108	68	40	
T. D., 32	For hernia	Tropacocaine, '014 gms.	84	57	Regular	130	78	52	Very nervous.
T. C., 21	For varicocele	Tropacocaine, '022 gms.	72	52	Regular	118	92	26	Pallor, sweating, shock.
H. F., 28	For hernia	Tropacocaine, '022 gms.	60	68	Regular	127	95	32	
J. M., 18	For hernia	Tropacocaine, '014 gms.	60	48	Regular	122	105	17	Bad anæsthesia.
G. B., 69	Applying splint to fractured femur	Stovaine, 6 cgrs.	84	80	Regular	144	124	20	Good anæsthesia, sleeping at end.
F. B., 15	For hydrocele	Tropacocaine, '022 gms.	76	58	Regular	110	92	18	
K. B., 30	For varicose veins	Tropacocaine, '044 gms.	56	58	Irregular	120	104	16	Pallor.
C. H., 34	For double hernia	Tropacocaine, '022 gms.	74	48	Irregular	130	75	55	Pallor and some lividity.
G. K., 35	For hernia	Tropacocaine, '044 gms.	60	40	Irregular	112	62	50	Sweating, lividity, nausea.
D. L., 67	Prostatectomy	Tropacocaine, '022 gms.	60	66	Regular	170	58	112	Aortic regurgitation, pallor, shock.
E. B., 16	For varicocele	Tropacocaine, '022 gms.	64	68	Irregular	118	68	50	

In all of these cases it will be seen that there was a fall of blood pressure below normal at some time during the anæsthesia. The cases of stovaine are too few to form any estimate of its relative safety compared with that of tropacocaine, the only other drug employed, but, on the whole, it would appear to produce a smaller fall in blood pressure, and to cause less disturbance of the circulatory system in general.

The average fall in the 4 stovaine cases was equal to 16 mm. hg., and in the 13 tropacocaine cases it was equal to 39 mm. hg. The greatest fall under stovaine was 27mm. hg., and in tropacocaine, 112 mm. hg.; this latter was, in great measure, due to shock, but it is seen in 4 other cases, in which tropacocaine was injected, that the blood pressure fell 50 mm. hg. or more. This fall was, in the large majority of cases, accompanied by a slow and feeble pulse; in 5 of the 13 cases in which tropacocaine was given, the pulse became irregular, and in a large proportion became exceedingly slow. There was a tendency to develop pallor in the majority of cases, while in 3 of the cases in which tropacocaine was injected there was distinct lividity of lips and nose. There appeared to be a marked idiosyncrasy in the action of the drugs on different patients, both in the production of anæsthesia and in the effect on the blood pressure; there was no very definite relation between the size of the dose and the effects produced.

The effect of shock was very evident in one case, and would appear to have been a contributing factor in one or two other cases; it cannot, therefore, be claimed for spinal analgesia any more than for general anæsthesia that it eliminates this danger, but it would rather appear that the agents employed have, in themselves, the property of producing shock under certain conditions of dosage and idiosyncrasy.

The fall in blood pressure may be due in some measure to the quietening effect on respiratory movements, but is due, in the main, to the inhibitory effect on the splanchnic nerves, the removal of their tonic vaso-motor action, and the consequent engorgement of the area they supply. This inhibitory action is

the direct outcome of the drug's toxic properties on the nerve roots, and on the vaso-motor centre itself, and would appear to be the great danger of this form of anæsthesia. The posture usually adopted to prevent the spread of the drug to the centres in the medulla tends to produce splanchnic stasis, through the influence of gravity, while the depressing action of the drug on the vaso-motor centre renders it inadvisable to resort to the postural methods that are commonly serviceable in shock during general anæsthesia. So great is the dread of the inhibitory action of the various drugs on the vaso-motor centre that, until recently, it has been customary to perform the injection in the lumbar region, and not to attempt anæsthesia beyond the level of distribution of the fourth dorsal nerve.

It is now, however, claimed by Jonnesco and others that anæsthesia can be safely and satisfactorily produced for operations on the head and neck by spinal injections of stovaine in the upper cervical region, the danger of serious involvement of the vaso-motor centre being avoided by the addition of strychnine. As far as can be gathered from the limited number of published results of this mode of administration, there is still much to be desired from the point of view of anæsthesia, while it would appear to be a somewhat hazardous experiment, especially as the action of strychnine in the maintenance of blood pressure is extremely doubtful, and at all events in the presence of shock is probably actually harmful. To rely on strychnine alone to prevent the onset of that grave fall of blood pressure, that is acknowledged to be the main feature of surgical shock, would seem to court disaster. It has already been seen that spinal anæsthesia does not eliminate shock, and it is in cases of this nature that the action of strychnine might be not only useless but actually disastrous. The only remedy that would appear to hold out any hope would be one that would maintain the blood pressure by direct tonic action on the heart and the muscular walls of the peripheral vessels. This power is possessed by various preparations made from the suprarenal glands, but the transitoriness of their action makes their application diffi-

cult. Extract of the infundibular portion of the pituitary gland, owing to its more lasting effect, promises to be of great service in this condition, and may possibly be instrumental in greatly increasing the safety and usefulness of spinal analgesia.

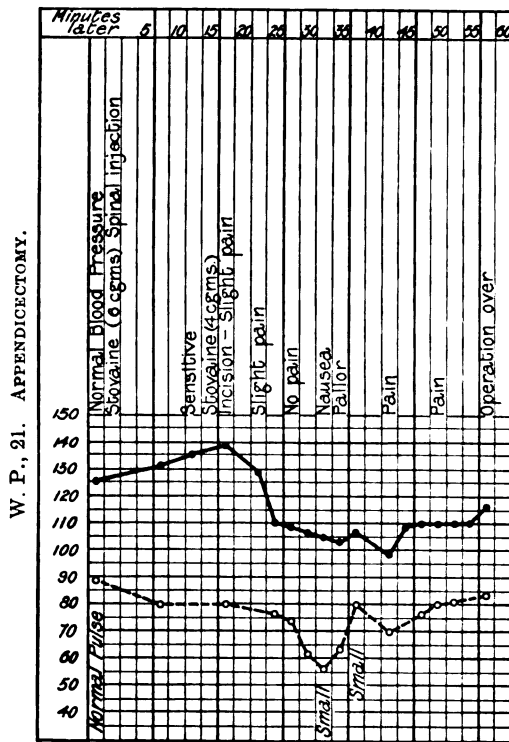


CHART 8.—Showing the action of stovaine on the pulse and blood pressure.

The treatment of shock and collapse has, in the past, been attempted with a number of remedies, without sufficient attention being paid to the physiological factors that produce the conditions. In a previous portion of this paper the conditions themselves have been defined, and the various factors that produce them discussed.

The suggestion is made by Malcolm and other observers that shock is not produced by exhaustion of the vaso-motor centre

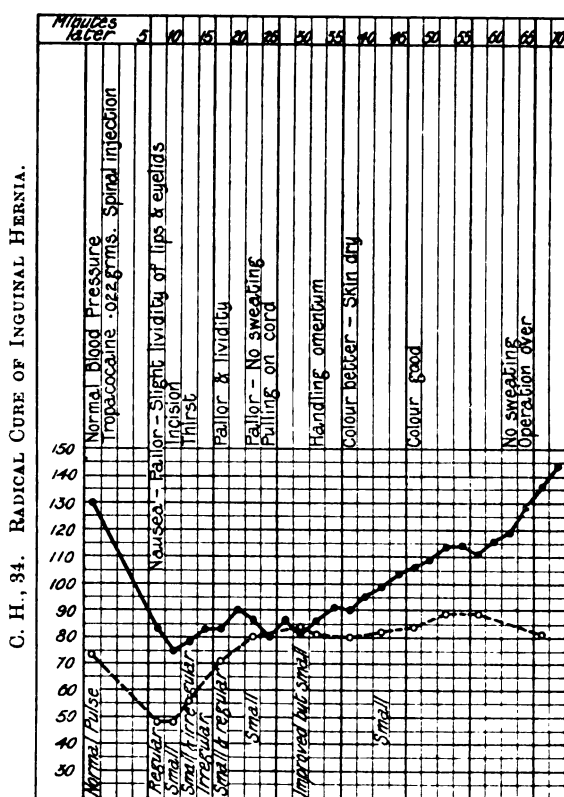


CHART 9.—Showing the action of tropacocaine on the pulse and blood pressure.

and a consequent dilatation of the peripheral vessels, but by an exaggerated contraction of the general vascular system, "which at once raises blood pressure in the large arteries and lowers it in the small arteries."* The results of Crile's experiments, however, and the general experience of others, is that the action of the vaso-dilators, such as amylnitrite, tends to increase shock, whereas the effect of vaso-constrictors, such as suprarenal and pituitary extract, have a distinctly beneficial effect. Moreover, the statement that during shock the pulsation in the large arteries—for example, in the carotid—is more forcible,

* Malcolm, Clinical Journal, September 1st, 1909.

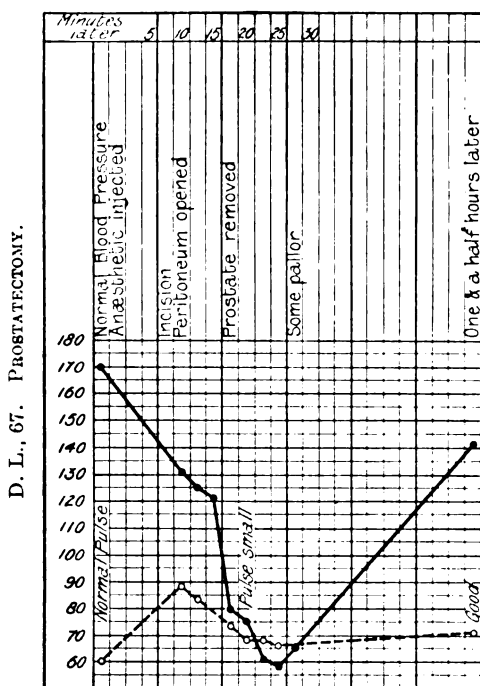


CHART 10.—Showing the action of shock on the blood pressure under tropacocaine.

and that therefore the blood pressure is, *ipso facto*, raised, is misleading, for it would appear rather that the apparent increase in force depends rather on the general muscular flaccidity, and on the fact that during systole the heart is driving blood into empty vessels, the effect being much the same as that produced on a sail by a puff of wind during a calm as compared with the action of a steady breeze. It was possible in one case suffering from severe shock* to examine the abdominal artery directly at a time when the blood pressure was lowest in the radial artery; in this case the pulsation in the aorta was only just perceptible, so that the surgeon had considerable difficulty in assuring himself of its identity. We may assume, therefore, that shock is due to exhaustion of the vaso-motor centre, with consequent

* See Chart 11.

dilatation of the peripheral vessels, especially in the splanchnic area. It is, then, obvious that stimulants, such as strychnine, though they may be of service in cases of collapse, where the centres are not exhausted, can be of no use in shock, and are probably harmful. It can be of no use to look to the exhausted vaso-motor centre for relief, the only possible remedies being those supplied by gravity in a suitable posture, such mechanical measures as bandaging the extremities and abdomen, or the pneumatic suit, transfusion with normal saline, or the introduction of some agent into the blood stream that will act directly on the heart and muscular coat of the peripheral vessels, causing an increased force in the heart beat and a rise in the general arterial pressure.

The influence of posture has already been considered, and may be included under the same category as the more mechanical remedies, which have a distinct, but somewhat limited, usefulness, as their adoption is obviously not possible in all cases. The intravenous injection of normal saline has an immediate effect on the blood pressure,* while in the subcutaneous and rectal injections its action is more gradual; in cases of severe shock, when the circulation has become very feeble, it is unlikely that infusion other than intravenously can be of any service. The value of intravenous injection depends partly on the fact that it raises the amount of fluid circulating, and thus directly increases blood pressure and stimulates the heart's action, but also on the fact that it lessens the viscosity of the blood, which always becomes much increased in cases of severe shock and collapse. In cases of collapse, it undoubtedly has immense value, but in cases of severe shock, where the vaso-motor centre is unable to take up its duties, the saline solution rapidly passes from the relaxed peripheral vessels as a profuse sweat, or into the connective tissues of the abdomen, where it may, if considerable, seriously embarrass the movements of the diaphragm.

It would seem reasonable, therefore, in cases of severe shock, to attempt to stimulate the peripheral vessels to contract by

* See Chart 11.

directly acting on the vessels themselves, and thus to give a more lasting effect to the benefit derived from saline infusion. The discovery of the properties of extracts of the suprarenal gland opened up great possibilities in this direction, but were found to be of somewhat limited usefulness, on account of the transient effect of their action. More recently investigations have been carried out with regard to the influence of the pituitary gland on blood pressure, and it has been found that its action is very similar to and much more lasting than that of the suprarenal gland. In a series of 7 cases an extract of the pituitary gland was injected at different times during and immediately after the administration of various anæsthetics. The dose given in 6 cases was equal to 0.2 gramme of the fresh posterior lobe of the pituitary body, and in the remaining case was half this amount. The following is a list of the cases :—

Initials and Age.	Operation.	Anæsthetic and duration.	Dose of Pituitary extract.	Effect on Blood Pressure in mm. Hg.	Latent Period.	Site of Injection.	General Condition, etc.
L. H. 20	Excision of gut	Ether 75 min.	0.2 gm.	+ 26	Min. ?	Subcut.	Injection after severe operation. Blood pressure raised for over eighteen hours.
W. C. 15	Opening shoulder	Ether and morphia 40 min.	0.2 gm.	+ 30	15	Subcut.	Experimentally at end of operation. Blood pressure raised for three days
M. H. 41	Abdominal hysterectomy	Ether and A.C.E. 100 min.	0.2 gm.	?	?	Subcut.	Given during severe collapse. No apparent result for half-an-hour. Good recovery.
M. F. 44	Excision of breast	A.C.E. 70 min.	0.1 gm.	+ 20	10	Subcut.	Given early in severe operation appeared to prevent shock. Blood pressure much raised on following day.
A. D. 20	Exploring cerebellum	A.C.E. and ether 40 min.	0.2 gm.	+ 46	1—2	Intravenously.	Severe operation; injection, followed by immediate rise. Blood pressure high on following day.
H. 24	For double talipes	Ether 65 min.	0.2 gm.	+ 12	5	Subcut.	Given experimentally. Slight rise, which continued some hours.
A. G. 48	Excision of kidney	Ether and chloroform 140 min.	0.2 gm. or + 52	+ 30 or + 52	1—2	Intravenously	Given during severe shock with saline infusion. Considerable rise. Died thirty-six hours later (secondary hemorrhage).

In every case there was a distinct rise of blood pressure following the injection, which was more rapid in its onset and of greater extent when the injection was directly into a vein. The effect on the pulse was to increase its force and to diminish its rate, at the same time steadying it when there was irregularity.

In cases of shock, where the circulation has been reduced to a very low ebb, subcutaneous injection would appear to have little immediate effect, whereas the intravenous injection with saline solution produced a rapid rise of blood pressure, which was maintained for some hours.*

* See Chart 11.

Pituitary extract was injected subcutaneously in one case on account of severe post-operative shock having occurred on two previous occasions; in this case the blood pressure rose to a point 20 mm. hg. above normal in 20 minutes, and remained considerably raised for more than 18 hours. The patient made an excellent recovery, and had no sign of shock or collapse, though the operation was severe, and her condition bad before it was commenced.

The blood pressure was estimated in 4 cases the day after operation, and was in each case found to be considerably raised: there were possibly contributory factors in the production of this condition, but its extent and the general well-being of the patients were unusually marked.

The general impression given by these few cases is that, if injected early, it reduces the risk of shock during severe operations, and materially lessens the occurrence of serious depression afterwards; all the patients in this series except one, who died 36 hours after the operation from the effects of very profuse hæmorrhage, made exceptionally rapid recoveries, in spite of the fact that the operations were severe, and that in one patient profound shock occurred some time before the completion of a difficult hysterectomy.

The experiments of Bell and Hick* seem to show that one of the results following the injection of pituitary extract is an increase of calcium salts in the blood, and to this may possibly be due its continued tonic action on the heart and peripheral vessels. They have further shown that a very large amount of calcium is excreted during menstruation, and that towards the end of pregnancy the calcium content of the blood is considerably increased.† This is an interesting fact in connection with the general experience that chloroform anæsthesia during parturition is comparatively safe. Further investigations of theirs have shown that one of the functions of the thyroid gland is to stimulate calcium secretion, and it may be inferred that this is a factor in determining the danger experienced during anæsthesia in patients suffering from a hypersecretion of this gland.

* *British Medical Journal*, February 27th, 1909.

† *British Medical Journal*, March 27th, 1909.

Calcium salts undoubtedly raise the blood pressure, at the same time increasing the force and diminishing the rate of the heart beat, and would appear to offer considerable possibilities in those cases of low blood pressure in which serious operations are contemplated.

A. G., 48. EXCISION OF KIDNEY.

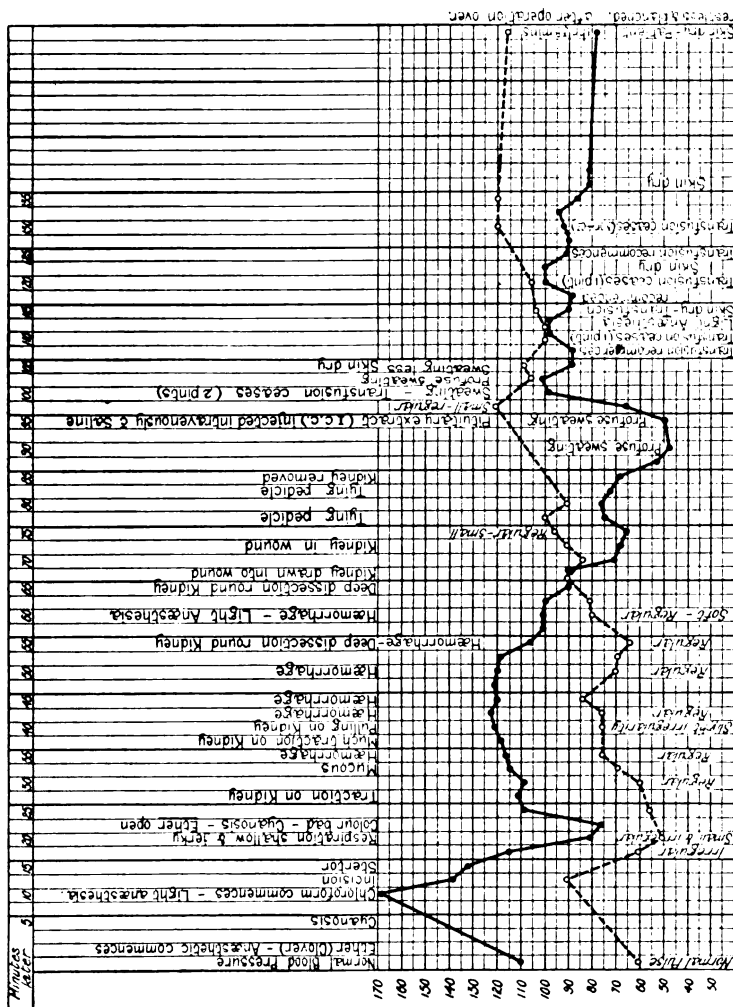


CHART 11.—Showing rapid rise of blood pressure under ether with respiratory obstruction, followed by sudden fall under chloroform, and further rise under ether; later collapse following hæmorrhage, and effect of saline infusion and pituitary extract. This observation was of great service in making it possible to regulate the infusion of saline solution so as to maintain sufficient blood pressure to complete the operation.

SUMMARY.

The chief danger of anæsthesia is admittedly a serious and progressive fall of blood pressure; the maintenance of blood pressure, therefore, becomes a matter of vital necessity. In chloroform administration the danger is due to the depressing action of the drug on the tissues, whereas in ether it rather lies in over-stimulation and subsequent exhaustion; hence, it follows that an undue concentration of anæsthetic vapour is of much greater immediate danger with chloroform than with ether. In the case of each the danger is markedly lessened by the gradual and even distribution of the drug throughout the tissues, and by the avoidance of any respiratory obstruction or struggling. The percentage administration of chloroform would appear to present many advantages, though it can never be expected to eliminate the danger of a sudden overdose, seeing that the amount of chloroform in the alveolar air depends upon the freedom of the intake, and not merely upon the strength of the vapour.

The fall of blood pressure during chloroform anæsthesia has been described as conservative, and as being an attempt on the part of the organism to prevent the further diffusion of the drug throughout the tissues; it would seem rather to be intrinsically destructive, and to be part of a general inhibition of vital processes. This conclusion is supported by the recent investigations of Whipple and Sperry in the Johns Hopkins University, who have shown that chloroform anæsthesia in animals invariably produces extensive pathological changes in the tissues, notably in the liver, heart, and kidneys.

The pressor action of ether on the circulation is undoubtedly the main factor in its comparative safety, and in the prevention of surgical shock, which is so marked a feature of its administration in serious operations.

The influence of spinal analgesia is to considerably lower the blood pressure, the serious disadvantage being that there is marked idiosyncrasy displayed in its action on different patients,

while the maintenance of the blood pressure and the limitation of the spread of the drug's action are mutually antagonistic. Both in spinal analgesia and in general anæsthesia, where a serious fall of blood pressure is to be feared, it would seem likely that the injection of pituitary extract offers the best means of avoiding the trouble.

The investigations that have resulted in the materials from which this paper is drawn have increasingly deepened the conviction that the maintenance of arterial blood pressure is all-important in the production of safe anæsthesia. They have further demonstrated the great service of accurate observations of the blood pressure during anæsthesia, both in the early recognition of impending danger, and in the control of serious conditions when they have supervened.

F. W., 34. RADICAL CURE OF HYDROCELE.

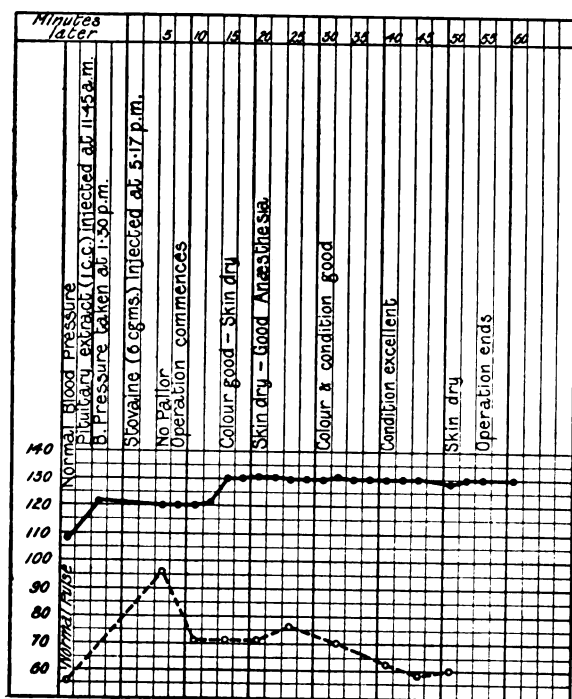


CHART 12.

NOTE.—Since writing the above paper, I have, in three cases of spinal analgesia, injected 1 c.c. of pituitary extract some hours before the operation, with a view to prevent the fall of blood pressure that invariably accompanies this form of anæsthesia. In two of the three cases the anæsthesia was unsatisfactory, the operation being attended with some pain and vomiting, and there was a distinct fall of blood pressure in each case while the gut was being handled; this fall, however, was only temporary, and was followed by a rise of blood pressure above normal. In the third case, in which the anæsthesia was good, the blood pressure remained above normal throughout, and was not influenced either by the anæsthetic nor by manipulation of the testicle. This is the only case of spinal analgesia in which the blood pressure record does not show a considerable fall, and would appear to denote that pituitary extract has a distinct influence in preventing the depressor effect that is due to the anæsthetic.

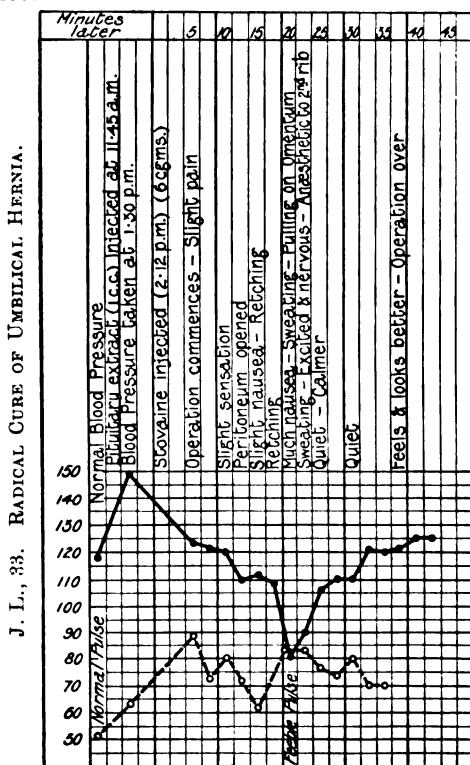


CHART 13.

LIST

OF

GENTLEMEN EDUCATED AT GUY'S HOSPITAL

WHO HAVE PASSED THE

EXAMINATIONS OF THE SEVERAL UNIVERSITIES, OR OBTAINED

OTHER DISTINCTIONS, DURING THE YEAR 1909.

University of London.

Examination for the Degree of Doctor of Medicine.

Branch I.—*Medicine.*

H. I. Janmahomed (Gold Medal) | E. F. Milton

Branch IV.—*Midwifery and Diseases of Women.*

P. W. Hamond

Examination for the M.B., B.S. Degrees.

May.

Honours.

A. H. G. Burton (Distinguished in Medicine).

Pass.

L. T. Baker	J. L. Johnston	W. P. Purdom
L. Croft	H. C. Lucey	R. A. Rankine
S. J. Darke	H. E. H. Mitchell	St. J. A. M. Tolhurst
T. Evans	W. P. H. Munden	C. A. Wood
F. W. Hogarth	J. R. Perdrau	

Supplementary Pass List.

Group II.—*Surgery, Midwifery, and Diseases of Women.*

P. D. F. Magowan

Third (M.B., B.S.) Examination for Medical Degrees.

October.

Honours.

(d) M. A. E. Duvivier | (d) G. H. Peall
(d) *Distinguished in Surgery.*

Pass.

M. E. Ball	M. R. Dobson	A. A. Greenwood
R. P. Ballard	R. C. V. Edsall	E. L. W. Mandel

Supplementary Pass List.

GROUP I.—*Medicine, Pathology, and Forensic Medicine.*

H. W. Catto | E. L. Elliott

GROUP II.—*Surgery, Midwifery, and Diseases of Women.*

T. Stansfield

Intermediate Examination in Medicine.

January.

C. Aldis	V. Glendining	T. T. O'Callaghan
B. Blackwood	H. L. Hopkins	*B. R. Parmiter
G. Covell	G. Marshall	H. P. Warner
G. T. Foster-Smith	P. J. Monaghan	

**Distinguished in Physiology.*

Second Examination for Medical Degrees.

Part I.

July.

Organic and Applied Chemistry.

J. R. Barrow-Clough	C. S. L. Roberts	*A. J. E. Smith
G. D. Eccles	H. C. Rook	A. Wills
G. S. Miller	E. D. Scott	O. R. L. Wilson
C. E. Petley	C. Sherris	

**Awarded a mark of distinction.*

Part II.

D. A. Davies | G. E. Genge-Andrews | W. S. George

Preliminary Scientific Examination.

January.

Part I.

Inorganic Chemistry and Experimental Physics.

A. J. E. Smith

Inorganic Chemistry and Biology.

S. S. B. Harrison | D. M. MacManus

Experimental Physics and Biology.

(c) W. L. Gwyn Davies	(c) F. H. Dodd	(c) W. L. E. Reynolds
	(c) L. M. Smith	

Experimental Physics only.

(c) S. H. Robinson	(cb) J. A. Ryle
--------------------	-----------------

Biology only.

(cp) G. D. Eccles	(cp) H. W. Evans	(cp) R. O. H. Jones
-------------------	------------------	---------------------

(b) *Has already passed in Biology.*

(c) *Has already passed in Organic Chemistry.*

(p) *Has already passed in Experimental Physics.*

Part II.

Organic Chemistry.

T. I. Bennett		S. Keith		W. Robinson
R. Creasy		J. F. G. Richards		A. L. Shearwood
		H. Webb		

First Examination for Medical Degrees.

Inorganic Chemistry, Physics, and General Biology.

July.

F. C. S. Broome		†H. C. Hitchings		H. P. Whitworth
*C. H. Gould		J. York Moore		
* <i>Distinction in Biology.</i>			† <i>Distinction in Physics.</i>	

The following Students who took a portion of the Examination under the Old Regulations have now completed it :—

F. V. Bevan-Brown		S. S. B. Harrison		D. M. MacManus
		S. H. Robinson		

December.

P. D. Scott		R. S. Stewart		A. L. Stokes
		H. Q. F. Thompson		

University of Oxford.

Second M.B. Examination.

Forensic Medicine and Public Health.

G. H. Hunt

University of Cambridge.

Degree of Doctor in Medicine.

W. H. Brailey		C. H. Rippmann		B. H. Stewart
G. H. K. Macalister		C. W. Ponder		

Degree of Doctor in Science.

H. E. Durham

Degree of Master in Surgery.

A. S. B. Bankart		C. W. Greene
------------------	--	--------------

Third Examination for the Medical and Surgical Degrees.

Part II.

L. Bromley	W. Ledlie	C. F. Searle
A. B. Carter	H. G. Rice	J. Walker
H. L. Duke	J. G. Saner	B. Wallis
	C. S. E. Wright	

Part I.

F. S. Adams	J. B. Hance
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Second Examination for the Medical and Surgical Degrees.

H. A. Ash	C. Warner	A. M. Zamora
-----------	-----------	--------------

University of Bucham.

Third Examination for the Degrees of M.B. and B.S.

H. L. James	J. H. Owen
-------------	------------

First Examination for the Degrees of M.B. and B.S.

R. P. Ninnis

Royal College of Physicians of London.

Examination for the Membership.

A. H. Miller, M.B., B.C. Cantab.

Final Examination for the Licence.

January.

M. M. Adams	A. A. Greenwood	J. R. Perdrau
D. Allan	H. Lee	R. A. Rankine
P. A. S. Dyson	A. E. Lees	W. E. Wallis
T. Evans	H. R. Mullins	F. J. Wheeler

April.

J. L. Atkinson	P. C. Field	A. C. Schulenberg
J. F. Brown	E. P. L. Hughes	C. F. Searle
R. B. Dawson	D. Isaacs	E. R. Stone
L. W. Evans	H. E. H. Mitchell	

July.

S. S. Brook	F. J. Cutler	A. L. Fitzmaurice
M. M. Cowasjee	H. L. Duke	H. W. Heasman
C. H. Crump	M. A. E. Duvivier	W. Ledlie
	C. G. Sprague	

October.

H. L. Attwater	D. C. Druitt	W. L. Hibbert
S. H. Browning	E. Elliott	W. S. Kidd
A. E. P. Cheesman	R. C. H. Francis	C. H. Mills
E. A. Collins	G. F. Haycraft	D. A. Mitchell
	G. H. Peall	

Royal College of Surgeons of England.

Final Examination for the Fellowship.

A. S. B. Bankart	T. B. Layton	C. F. L. Leipoldt
	L. C. Panting	

Primary Examination for the Fellowship.

V. Glendining	N. Mutch	W. E. Tanner
W. H. Miller	E. G. Schlesinger	A. H. Todd

Final Examination for the Membership.

January.

M. M. Adams	A. A. Greenwood	J. R. Perdrau
D. Allan	H. Lee	R. A. Rankine
P. A. S. Dyson	A. E. Lees	W. E. Wallis
T. Evans	H. R. Mullins	F. J. Wheeler

April.

J. L. Atkinson	P. C. Field	A. C. Schulenberg
J. F. Brown	E. P. L. Hughes	C. F. Searle
R. B. Dawson	D. Isaacs	E. R. Stone
L. W. Evans	H. E. H. Mitchell	

July.

S. S. Brook	F. J. Cutler	A. L. Fitzmaurice
M. M. Cowasjee	H. L. Duke	H. W. Heasman
C. H. Crump	M. A. E. Duvivier	W. Ledlie
	C. G. Sprague	

October.

H. L. Attwater	D. C. Druitt	W. L. Hibbert
S. H. Browning	E. Elliott	W. S. Kidd
A. E. P. Cheesman	R. C. H. Francis	C. H. Mills
E. A. Collins	G. F. Haycraft	D. A. Mitchell
	G. H. Peall	

Final Examination for the Licence in Dental Surgery.

May.

C. H. Brangwin	P. R. Helvar	H. G. Spain
N. D. Clarke	D. Y. Hylton	J. A. W. Stuart
A. Cohen	R. C. Morgan	A. M. Watson
F. L. Furse	G. H. Rowley	

November.

C. H. Bradnam	P. S. Humm	P. H. Orton
F. B. Bull	L. J. Kemp	J. M. Pomeroy
T. L. Fiddick	C. G. Morris	R. W. Powell
J. D. George	W. C. Miller	J. Roberts
	H. Thornton	

College of Surgeons in Ireland.

Examination for the Fellowship.

C. L. G. Chapman

Conjoint Examining Board in England.

Diploma of Public Health.

H. B. Bolus, M.B., B.C. Cantab.

A. B. Carter, M.B., B.C. Cantab.

T. E. Holmes, M.D., B.C. Cantab.

Medical Department. Royal Navy.

K. H. Hole

| R. P. M. Roberts

| C. G. Sprague

G. F. Syms

Royal Army Medical Corps.

P. C. Field

| V. P. Hutchinson

| A. G. Jones

H. F. Joynt

Indian Medical Service.

K. J. Kolaporewala

| M. A. Rahman

| H. Stott

MEDALLISTS AND PRIZEMEN,

JULY, 1910.

Open Scholarships in Arts.

Henry Francis Thomas Hogben, Bedford Grammar School	} equal, £50 each.
William Morris Lansdale, St. Olave's & St. Saviour's Grammar School	
James Kyle, Shrewsbury School, £50.	

Open Scholarships in Science.

Charles Hamilton Gould, Preliminary Science Class, Guy's Hospital, £150.
 James York Moore, Preliminary Science Class, Guy's Hospital, £60.
 Cyril Henry Edwards, St. Paul's School, West Kensington } equal,
 Allan Noel Minus, Thetford Grammar School } Certificates.

Scholarship for University Students.

Trevor Braby Heaton, B.A., Christchurch, Oxford, £50.

Open Scholarships in Dental Mechanics.

October, 1909, Reginald Gilbert Farrington	} equal, £10 each.
Douglas Wain	
May, 1910, Charles Henry Housden	} equal, £10 each.
Edgar Roskelly Williams	

Junior Proficiency Prizes.

John Frederick Gwyther Richards, £20.
 Oscar Reginald Lewis Wilson, £15.
 George Sefton Miller } equal,
 William Robinson } £5 each.

The Beaney Prize for Pathology (1909).

Albert Harold Godwin Burton, £34.

The Beaney Prize for Pathology (1910).

John Godfrey Saner } equal,
 Alan Herapath Todd } £17 each.
 Geoffery Dunderdale, Certificate.

The Michael Harris Prize for Anatomy.

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The Hilton Prize for Dissections (1910).

Skene Keith	}	equal,
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*Dental Prizes.**First Year's Prize in Dental Subjects.*

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Isidore Gittleson Samuels		£3 6s. 8d. each.
Reginald Douglas Tanner		

Second Year's Prize in General Subjects.

Alfred Thomas Rycroft, £10.

Harold Harrison	}	equal
Edward Palmer Hudson		Certificates.

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John Hargrave Rhodes, £10.

Newland-Pedley Gold Medal for Practical Dentistry.

Harold Harrison

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Treasurer's Gold Medal for Clinical Medicine.

Thomas Duncan Macgregor Stout.

Treasurer's Gold Medal for Clinical Surgery.

Harold Gardiner.

The Astley Cooper Prize.

Professor E. H. Starling, M.D., F.R.S.. £300.

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Session 1909-1910.—The Society's prize of £10 for the best essay read during the Session was awarded to Mr. N. Mutch, for his paper on "Appendicitis."

Mr. Frank Cook gained the Treasurer's prize of £5 for his paper, "On the Etiology and Pathology of Pigmentation in Constitutional Disease."

Mr. H. L. James gained the Society's prize of £5 for showing the best specimens of scientific interest during the Session.

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LIST OF ORIGINAL PAPERS BY MEMBERS OF GUY'S STAFF

CONTRIBUTED TO THE MEDICAL PRESS DURING
THE YEAR.

J. H. BADCOCK, M.R.C.S., L.R.C.P. Lond., L.D.S. Valedictory Address to the British Society for the Study of Orthodontia. *The Dental Record*, February, 1909.

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- M. S. PEMBREY, M.D. Oxon.; A. P. BEDDARD, M.A., M.D. Cantab., F.R.C.P. Lond.; and E. I. SPRIGGS, M.D. Lond., F.R.C.P. Lond. The Relation of Acidosis to the Carbon Dioxide of the Blood in Diabetic Coma. *The Lancet*, June 19th, 1909.
- M. S. PEMBREY, M.D. Oxon.; HERBERT FRENCH, M.D., F.R.C.P.; and J. H. RYFFEL, M.B. Observations on Cases of Cyanosis due to Congenital Heart Disease. *The Journal of Physiology*, July 23rd, 1909.
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G. BELLINGHAM SMITH. M.B., F.R.C.S. Eng., and J. W. H. EYRE, M.D., M.S., F.R.S. A Clinical Lecture on Septicæmia and its Modern Treatment. *The Clinical Journal*, September 8th, 1909.

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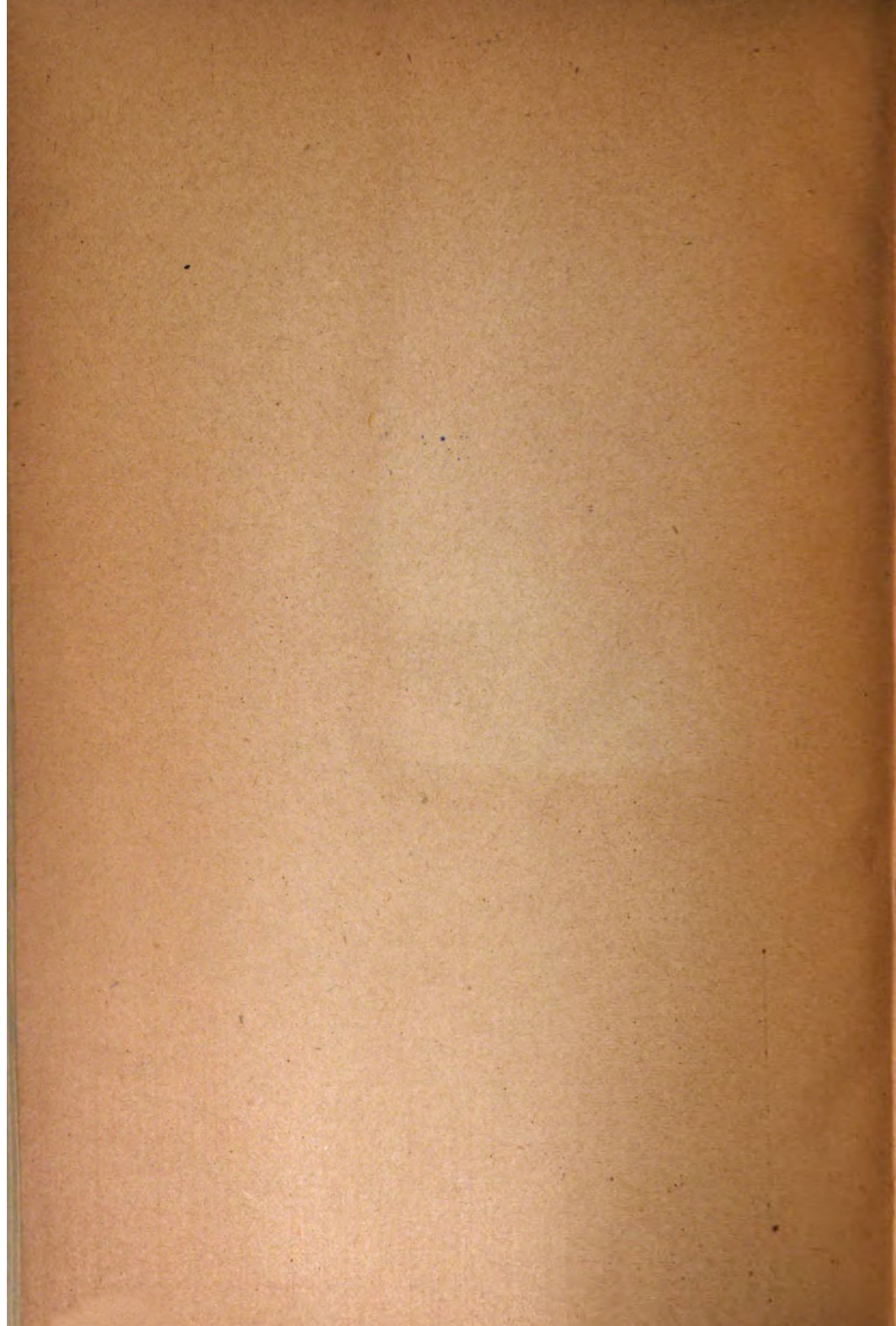
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Dental Appointments held during the year 1908.
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